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CONTENTS Page

Editorial

- Artificial intelligence foundation models in healthcare: A Malaysian perspective 1
  Shen-Han Lee, Irfan Mohamad

Original Articles

- Competency in chest X-ray interpretation: Variations across medical experiences and training levels 6
  Koa Ai Jiun, Cheah Whye Lian, Yew Ting Ting, Ahmad Tirmizi Jobli
- Evaluating the efficiency of one stop crisis centres in managing domestic violence cases 13
  Ke Lin Siew, Shirly Siew-Ling Wong, Keng Sheng Chew, Vanitha Kandasamy, Aida Bustam, Muhammad Izzat Abdul Hadi
- Factors associated with the practice of home blood pressure monitoring among healthcare providers in public healthcare clinics in Putrajaya 19
  Noor Faridzatul Ain Mohd Noor, Aneesa Abdul Rashid, Muhamad Fikri Shazlan Saad
- Developmental and emotional behavioural outcomes after COVID-19 febrile seizures: A single-centre experience 27
  Jun Jean Ong, Xiang Lin Cheng, Michelle Chok, Juliana Hashim, Yong Xin Choo, Muhammad Ihsan Roslan, Yeen Zou Gan, David Chun-Ern Ng
- Association between irregular eating habits and irritable foods with dyspepsia syndrome in students 34
  Trini Suryowati, Stella Sophia Kwannandar, Tiroy Sari B Simanjuntak
- A retrospective study on patterns of acute chemical poisoning in an urban tertiary hospital in Malaysia 41
  Nur Hafizah Hamzah, Ariff Arithra, Junainah Nor
- Comparing the administration of rt-PA among stroke fast track patients who arrived by emergency medical services and non-emergency medical services 48
  Sirinapa Saneemanomai
- Job insecurity and psychological wellbeing among junior doctors in Malaysia: A national cross-sectional study 53
  Siow Sze Li, Chuah Jun Sen, Sentilnathan Subramaniam, Hans Alexander Mahendran, Mohamad Adam Bujang, Kok Juan Loong
- Open-window thoracostomy in empyema thoracis: A retrospective review 62
  Ehab Said, Narasimman Sathiamurthy, Benedict Dharmaraj, Narendran Balasubbiah
- Custodial HTK Cardioplegia in conventional cardiac surgery: A retrospective analysis From UiTM 70
  Tuan Muhammad Syukri Tuan Kob, Anas Kasran, Wan Mohamad Afham Wan Jusoh, Muhammad Juffri Samsuddin, Allim Khairuddin, Raja Amin Raja Mokhtar
- Prevalence and factors associated with seizures among patients with infective encephalitis 74
  Fathimath Mohamed, Juen Kiem Tan, Rathika Rajah, Ching Soong Khoo, Michelle Maryanne Tan, Rosnah Sutan, Muhammad Samir Haziq Abd Rahman, Mohamed Nafiz Ahmed, Hui Jan Tan
- Measles in Selangor: A Comparative Analysis Between Adults and Children Using the E-Measles Registry, 2015-2024 84
  Nurul Safiyah Ismail, Mariam Mohamad, Faridah Kusnin, Sharifah Malihah Wan Mustapha, Leny Suzana Suddin

CONTENTS Page

- Outcome of Hepatitis C Screen-and-Treat Program at a Drug Rehabilitation Centre in Perlis State 92
  Nurkhaniza Kaman, Mohd Azri Mohd Suan, Abdullah Afifuddin Samsurizal, Rohemi Abu Bakar, Muhammad Radzi Abu Hassan

- Digital eye strain among library users: Prevalence and ROC-derived cut-off point for the DESRIL-27 98
  Nabilah Ayob, Mohammad Saffree Jeffree, Sharina Mohd Shah, Kamal Lazi, Edwin de Cruz, Azizan Omar

- Epidemiology of major trauma in Malaysia: Preliminary findings from the Malaysian Trauma Registry 105
  Ahmad Ibrahim Kamal Batcha, Shah Jahan Mohd Yussof, Rossman Hawari, Yeoh Chun Chiat, Christopher Aylwin, Shamila Mohamad Ali, Rathini Inthiran

- Effect of multi-strain probiotics on enhancing apoptosis in lung cancer cells A549 115
  Marisca Evalina Gondokesumo, Ronny Lesmana, Ge Recta Geson, I Gede Yudi Anggara, Aguslina Kirtishanti

- A descriptive evaluation of referral patterns and patient flow from Primary Health Facilities to the Emergency Department Hospital Sungai Buloh 123
  Sarah Shaikh Abdul Karim, Ahmad Amirin Jamal, Marzilawati Abd Rahman, Mahathar Abd Wahab, Azah Abdul Samad, Siti Aisyah Abd Majid, Norafizan Mohd Ali, Siti Suhaila Hamzah

- Survey of virtual ward acceptance among medical patients admitted to hospital 130
  Nai Shan Yeat, May Hun Tai, Amanda Goh, Muhamad Danial Zulkifli, Stephanie Ko, Terence Ong

- Genomic profiling of early-stage resectable non-small-cell lung cancer in a Malaysian private healthcare setting: Real-world clinical implications 136
  Anand Sachithanandan, Hoh Hong Huat, Lam Mynn Dee, Low Eng Chai, Yap Ning Yi, Siti Ayuni Hassanudin, Ten Yi Yang, Tan Pak Kheong, Naim Che Kamaruddin, Fatin Najihah Muhammad Lutfi, Yong Wong Wai Shieh, Shobana Satchithananthan, Yap Xuan Lin, Pathmanathan Rajadurai

- Clinical characteristics and factors affecting visual outcomes in patients with herpes simplex keratitis: A tertiary hospital experience 146
  Hawwa Najiza, Julieana Muhammed

- A Malaysian study on COVID-19 (SARS-CoV-2) vaccination immune response in haemodialysis patients: A prospective, multicentre, cohort study 152
  Xue Fang Tan, Chin Chin Ch'ng, Jie Ling Cheng, Ley Khim Teo, Adiratna Mat Ripen, Chen Hua Ching, Shahnaz Shah Firdaus Khan, Wan Hasnul Halimi Wan Hassan, Yew Fong Liew, Loke Meng Ong, Chee Kin Yoon

Systematic / Narrative Review Article

- The artificial intelligence driven on the development of diabetic retinopathy prognostic scoring tool among type 2 diabetes mellitus patients: A review 158
  Muhammad Muaz Shahriman Teruna, Tajul Rosli Razak, Siti Munira Yasin, Abdullah Ashraf Rafique Ali, Mohamad Rodi Isa

- Challenges in delivering healthcare services among immigrants from Southeast Asia: A scoping review 163
  Azulaikha Alias, Idzhar Azwan Mohd Idrus, Darryl Daring, Nurliyana Azhar, Wan Hafizu Wan Mohamad Lotfi, Abdul Rahman Ramdzan, Afiq Izzudin A Rahim

CONTENTS Page

- Closing the gaps in obesity: The need for a strategic, system-wide approach to obesity care in Malaysia 172
  Zubaidah Nor Hanipah, Masni Mohamad, Barakatun Nisak Mohd Yusof, Norlaila Mustafa, Firdaus Mukhtar, Wong Ping Foo, Nalini M Selveindran, Nazrul Hadi Ismail, Feisul Idzwan Mustapha, Rohana Abdul Ghani

- The role of apolipoproteins as genetic biomarkers in schizophrenia: A systematic review 180
  Wan Noorainna Fatimi Wan Mohd Zani, Nour El Huda Abd Rahim, Norlelawati A Talib, Mohd Asyraf Abdull Jalil, Mohd Arifin Kaderi, Norbaiyah Mohamed Bakrim, Wan Muhamad Salahudin Wan Salleh, Rinesh Ram Mohan, Norainin Sofiya Azman, Siti Norain Mat Rasid

- Accuracy of diagnostic performance of confocal laser endomicroscopy in characterising pancreatic cysts: A systematic review 195
  Abdullah Alotaibi

Short Communication

- Diagnostic yield of CTPA and Wells Score utilization in pulmonary embolism assessment: Experience from a Malaysian tertiary hospital 202
  Nur Fathihah Ahmad, Ahmad Razali Md Ralib

Letter To The Editor

- The spectrum of developmental and epileptic encephalopathies and their genetic heterogeneity are much broader than previously thought 205
  Josef Finsterer

Acknowledgement 207

Artificial intelligence foundation models in healthcare: A Malaysian perspective

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ABSTRACT

One of the most revolutionary breakthroughs in modern artificial intelligence research over the past decade has been the introduction of foundation models – deep learning models trained on extensive datasets that can be adapted to tackle a wide range of downstream tasks. The rise of foundation models has significantly accelerated the adoption of AI in healthcare where there is increasing digitalization, enabling the integration of medical imaging, clinical notes, and genomic data to provide a more holistic understanding of patient health and supporting personalized interventions. In this Editorial, we will explore how foundation models are catalysing insights in precision health and offer our perspective of how foundation models can be integrated into the Malaysian healthcare system. In addition, we will also highlight some of the issues concerning governance, ethical, regulatory and policy challenges of implementing these foundation models in the Malaysia.

KEYWORDS:
Artificial intelligence; Foundation models; Large language models; Clinician; Healthcare system; Malaysia

INTRODUCTION

One of the most revolutionary breakthroughs in modern artificial intelligence (AI) research are foundation models including large language models which have been in the limelight since the release of Chat Generative Pretrained Transformer (ChatGPT) by OpenAI in November 2022.[1] This watershed moment heralded the era of generative artificial intelligence in the public domain with its widespread use across all fields including medicine. In this Editorial, we will explore how foundation models are catalysing insights in precision health and offer our perspective of how foundation models can be integrated into the Malaysian healthcare system. In addition, we will also highlight some of the issues concerning governance, ethical, regulatory and policy challenges of implementing these foundation models in Malaysia.

1. What are Foundation Models?

AI, broadly defined, is the use of technologies to build computational systems capable of mimicking human cognitive function and intelligence. Generative AI, a subset of AI, are deep learning models that can be trained to create new data. The term "foundation model", first coined by the Stanford Institute for Human-Centered Artificial Intelligence in 2021, refers to a form of generative AI, defined as large-scale deep learning models with broad capabilities that are trained on extensive datasets in an unsupervised fashion and can be adapted (e.g. fine-tuned) to tackle a wide range of downstream tasks.[2] In essence, these generative AI models are flexible and broadly applicable across various domains.

The modern evolution of foundation models began with the milestone introduction of the transformer architecture in 2017, a design that uses self-attention to process sequences in parallel and capture complex data dependencies more efficiently than previous deep learning models, such as recurrent neural networks.[3] Transformers emulate human attention by learning to focus on key aspects of input data, thereby improving prediction accuracy across varied applications such as natural language processing and computer vision. Today, foundation models are built on generative deep neural networks using the transformer architecture and leverage the principles of masked language modelling to understand the data structure, and transfer learning to reuse this knowledge to boost their performance of a related task. In simple terms, these large-scale deep learning models are trained on very large amounts of data without being given explicit instructions (unsupervised learning), allowing them to learn general patterns of these data on their own. Once trained, these models can be further adapted (fine-tuned) to perform tackle a wide range of downstream tasks, rather than being built only for a single purpose. Well-known examples of foundation models include Generative Pre-trained Transformer (GPT),[4] Bidirectional Encoder Representations from Transformers (BERT),[5] Gemini,[6] Large Language Model Meta AI (LLaMA),[7] and DeepSeek.[8] Essentially, the original model serves as a base (hence the term "foundation") on which other functions can be built upon, in contrast to other AI systems specifically trained for a particular use. A glossary of AI terminology is listed in Table I.

The most widely recognized use of foundation models in healthcare is in natural language processing (NLP) through the use of large language models (LLMs). These models are trained on vast amounts of text data and can be adapted (fine-tuned) for specific tasks such as summarizing medical documents, answering questions, and organizing or classifying information.[9] The same approach has also been

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Table I: Glossary of AI terms

Term	Definition
Artificial Intelligence (AI)	The use of technologies to build machines and computers capable of mimicking human cognitive functions and intelligence
Generative AI	AI systems that are designed to create new content, such as text, audio, or images in response to user prompts, by learning patterns from existing data
Machine Learning	A sub-field of AI that uses statistical algorithms to learn and make predictions based on input data without explicit programming, thereby "learning from experience."
Deep Learning	A variant of machine learning that uses neural networks to extract higher features of unstructured data such as images, video, and text and provide a suitable output such as prediction or evidence for a decision. These neural networks simulate the complex decision-making abilities of the human brain.
Neural Network	An AI system inspired by the human brain that consists of a large set of interconnected computational units (akin to neurons). Neural networks can have hundreds of layers of these neurons, with each layer playing a role in solving problems related to complex tasks.
Natural Language Processing	A subfield of artificial intelligence that facilitates automated analysis of language using machine learning, enabling computers to understand and communicate with human language.
Foundation Model	Large-scale deep learning models with broad capabilities that is trained on extensive datasets in an unsupervised fashion and can be adapted (e.g. fine-tuned) to tackle a wide range of downstream tasks
Transformer	A deep learning architecture that processes sequential data using a mechanism called parallel attention that emulates human attention, learning to focus on key aspects of input data and capture their long-range dependencies more effectively than previous deep learning models. In essence, the model dynamically weighs the significance of different parts of the input data and process them in parallel, making them highly scalable to process large datasets efficiently.
Large Language Model	A deep learning model that is trained on text to perform natural language processing tasks.
Transfer Learning	A machine learning approach in which a model trained on one task is adapted to perform a different but related task, using less data and training time.
Masked Language Modelling	A form of learning where certain tokens in a sequence (e.g. words in a sentence) is masked and hidden, challenging the models to predict these tokens and thereby develop an understanding of language structure.
Token	A basic unit of a sequence, such as a word, amino acid, or gene, that serves as the fundamental input unit for a foundation model.
Embedding	A numerical representation of real-world objects (e.g. words) as a vector in a high dimensional space that machine learning and AI systems use to understand complex knowledge domains
Pre-training	The first step of transfer learning, in which a machine learning model is trained on a large dataset to learn general features.
Fine-tuning	The second step of transfer learning in which a pre-trained model is adapted to a specific task by training it on a smaller and task-specific dataset.
Zero-shot	The ability of AI models to perform a task without needing any specific training on that task.

extended beyond text to other types of data, including medical image pixels,[10] audio signal waveforms[11] and even biological sequences such as protein amino acid sequences.[12]

2. When Foundation Models meets Digital Health and Big Data

The rise of foundation models has dovetailed with the big data and digital health revolution to transform how patient data can be used to derive insights that help clinicians make better decisions and deliver more personalized healthcare, ranging from disease diagnosis and treatment to genomics and drug discovery. One of the most notable applications of foundation models in healthcare is in medical imaging where vision-based foundation models have been used to analyse medical images, in particular, from three areas of medicine: radiology,[13] pathology,[14] and ophthalmology.[15] The field is rapidly evolving field with the development of various vision language models trained on multi-centre CT scan images,[16] retinal images,[17] and pathology slides[18] that are capable of outperforming other baseline deep learning models on the same tasks.

In the case of electronic medical records (EMRs), foundation models have been used to predict patient outcomes, and identify disease risks and trajectory despite the complexity and heterogeneity of EMR datasets.[19–22] In public health, foundation models been deployed to analyze large-scale public health and geospatial data for disease surveillance and disease outbreak prediction.[23,24] In precision medicine, foundation models have been used to learn complex patterns in genomic datasets,[25] identify genetic markers for disease[26] and predict treatment responses at the single cell level.[27] In drug discovery, foundation models can accelerate drug discovery by predicting drug-target interactions, design drug molecules, and drug repurposing.[28–30]

3. How can we implement AI foundation models in Malaysian Healthcare?

Recently, the Malaysian Ministry of Health has announced plans to scale cloud-based clinic management systems to more than 2000 government primary care clinics nationwide and expand the reach of total health information system to more government hospitals.[31] The expansion of this digital health infrastructure is in line with the Malaysia's aspiration of implementing a national EMR system to achieve the 'One Patient, One Record' vision.[31]

In light of this national electronic health record initiative, we propose that foundation models, including but not limited to large language models, should be built into this cloud-based

framework and national EHR. These models will enable active processing of high dimensional, heterogeneous time-stamped health data from these EHRs. Once trained, these foundation models can generate multiple simulated future patient health timelines and estimate the probability of clinical events occurring within those trajectories (e.g. length of stay, adverse events, hospital readmission, ICU admission). These probabilities may serve as dynamic risk estimates and serve as an early warning system, and as new patient data becomes available, the risk estimates are automatically updated.

Large language models can be trained to learn patterns from EHRs, such as clinic notes and investigation results. Furthermore, unstructured text in EHRs such a radiology reports offer a wealth of real-world data, and large language models offer new ways of extracting clinical insights from these large sets of unstructured medical text. In practice, these clinical data can be 'tokenized' and foundation models can then be trained to predict what information is likely to come next based on past data. Once trained, these models can be used to predict patient outcomes such as risk of mortality during or after hospitalization, the need for ICU admission, hospital readmission, and prolonged hospital stays.[19] Such models could also potentially help to improve patient risk stratification, suggest targeted interventions, and allow hospitals to better predict resource requirements.[32] In the future, these models could also help us to better understand the aetiology and progression of disease.

4. Building Trustworthy and Appropriate Foundation Models that Conform to Standards

As the worldwide AI community move towards more advanced foundation models such as multimodal systems that can reason across both images and text, there are several challenges that the various stakeholders in Malaysia need to work together to address.

AI systems need to be trustworthy, appropriate, transparent, conform to standards, and be clear on the issue of liability – these are principles espoused by the UK National Health Service AI Lab and Health Education England,[33] and more recently, the 2025 Malaysian Medical Council (MMC) Guideline on the Ethical Use of Artificial Intelligence in Medical Practice.[34] To this end, standards needs to be established with regards to data governance and the digital infrastructure should support safe and scalable deployment. Furthermore, clinical validation and performance monitoring should also evolve alongside technology.

However, there are complex challenges of integrating foundation models such as LLMs into existing clinical workflows. LLMs have a tendency to generate inaccurate or nonsensical information, commonly known as 'Hallucinations'. As such, who would take responsibility for medical errors, particularly in the context of these "hallucination" by LLMs? There have been reports on real-world harms to patients who relied on layperson-facing applications of foundation models for self-triage of transient ischemic attacks. Such cases raise concerns about whether these models can safely be integrated into healthcare systems. Ultimately, the MMC guidelines stipulates that the responsibility and liability fall on the registered medical practitioner, and therefore clinicians should be aware of the limitations of these foundation models to safeguard patient safety.[34]

5. Governance of AI Systems

The variety of public and private healthcare institutional structures in Malaysia means that there is fragmented ownership of health data, governance, procurement and data stewardship arrangements. This poses a governance challenge because there is no single authority that 'owns' responsibility for AI systems deployed across these silos. Furthermore, data used to train or fine-tune foundation models may come from multiple institutions with inconsistent data quality and oversight standards. Moreover, most hospitals in Malaysia lack AI governance committees and AI leads. As such, foundation models may only enter clinical workflows through research projects, isolated pilot initiatives, and informal use by clinicians and risk becoming a 'shadow infrastructure' outside proper institutional oversight with no audit trail, institutional responsibility or mechanism to learn from errors.

6. Data-sharing and Protecting Patient Privacy

Most existing foundational models are trained on datasets that are geographically and demographically 'narrow', limiting their global representation, generalizability and effectiveness particularly in under-represented regions and populations. Yet, there are concerns regarding data-sharing across institutions and borders, as well as the need to protect patient privacy. Therefore, robust data-sharing frameworks should be in place to address these concerns. To this end, we wish to highlight an example from the Global RETFound consortium, a global collaboration led by the National University of Singapore, Chinese University of Hong Kong, Moorfields Eye Hospital and University College London, that involves more than 100 study groups across 65 countries to create the world's first globally representative foundation model in medicine, trained on over 100 million fundoscopy images.[35] This consortium employs two robust, adaptable data-sharing frameworks – firstly, using only synthetic data generation through local fine-tuning of a foundation model, with only sharing of model weights, and no exchange of real data. As such, this ensures that the source data remains within their originating institutions, ensuring data sovereignty. The second data-sharing framework allows the transfer of anonymized real data within a secure cloud-based platform, governed by stringent protocols and legally-binding agreements. The group has released a comprehensive framework of their study protocol and data-sharing structure, allowing the use of these resources by other medical specialties and study groups to create similar initiatives within their own domains.[35]

7. Evaluating Foundation Models in the Local Setting

Due to the black-box decision making of foundation models and real-world variability, it is difficult to use traditional clinical trials to evaluate the efficacy of these models. New standards for reporting clinical trial protocols and results to evaluate interventions with an AI component have been introduced.[36,37] In addition, there should be rigorous validation of these foundation models on local health data

using retrospective data, protocol-driven trials for using these foundation models for clinical decision support systems, and randomized clinical trials using prospective data.[38]

CONCLUSION

In the new age of AI, the rise of foundation models has rapidly accelerated various advances in precision medicine and public health, and is driven by healthcare digitalisation and the big data revolution. In turn, the large amount of data generated can be used to train these foundation models to tackle a wide range of downstream tasks including prognostication, risk stratification, and predictive analytics. To implement foundation models such as large language models against the backdrop of a national electronic medical record in Malaysia, there should be a national AI in healthcare steering committee that spans healthcare institutions across the public and private sectors, with data-sharing and patient privacy governed by robust legal, ethical, and regulatory frameworks.

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ORIGINAL ARTICLE

Competency in chest X-ray interpretation: Variations across medical experiences and training levels

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ABSTRACT

Introduction: Chest X-ray (CXR) remains one of the most commonly used diagnostic imaging tools in clinical practice. However, the accuracy and competency in reading and interpreting CXRs can vary significantly across different levels of medical practitioners, ranging from house officers to senior specialists. The purpose of this study was to assess competency in CXR interpretation among doctors at different stages of their medical careers.

Material and Methods: This is a cross-sectional study conducted using CXRs, which were displayed digitally. A total of 305 participants were recruited, including house officers, medical officers, and registrars in specialty training. A standard set of ten radiographs was chosen, and the participants were required to interpret the CXR in multiple-choice format. Data analysis was performed via IBM SPSS Statistics software, version 25.

Results: Clinical history improved the ability to accurately interpret CXR, with the percentage of participants who accurately interpreted CXRs increasing from 21% of participants who achieved high scores without clinical history to 63.6% of participants who achieved high scores with clinical history. The participants' field of interest and confidence level when reporting a CXR without history were associated with higher accuracy ($p<0.05$) when interpreting a CXR. However, when the clinical history was given to the participant, only the confidence level of the participant affected the final score of the CXR. There is no significant difference in the ability of doctors to interpret CXR despite the difference in seniority in practice; moreover, undergraduate exposure does not play a significant role.

Conclusion: Structured teaching, continuous practice, feedback and integration into clinical decision-making are the keys that translate to greater competency in CXR interpretation. Future researches should emphasize on multicenter approach as it enhances the generalizability of findings to a broader national context.

KEYWORDS:
Chest X-ray; accurate interpretation; clinical history

INTRODUCTION

Chest X-ray (CXR) remains one of the most commonly used diagnostic imaging tools in clinical practice, offering crucial insights into a wide array of medical conditions affecting the lungs, heart, and surrounding structures. Accurate interpretation of CXRs is essential for timely diagnosis, proper treatment, and effective patient care. However, the accuracy and competency in reading and interpreting CXRs can vary significantly across different levels of medical practitioners, ranging from medical students to senior specialists.[1]

This variation in competency may stem from several factors, including the level of formal training, clinical experience, and individual expertise.[1-4] While junior doctors typically possess limited exposure and experience in interpreting chest X-rays, more experienced clinicians, such as senior doctors or radiologists, are often more proficient because of their specialized training and years of practice.

pneumonia, tuberculosis, pulmonary edema, and lung cancer, studies exploring competency differences across various levels of medical practitioners remain limited. This gap highlights the need for a comprehensive understanding of how medical experience and training influence diagnostic accuracy, as well as the potential consequences of such variations on patient outcomes.

The purpose of this study was to assess competency in CXR interpretation among doctors at different stages of their medical careers. By evaluating the performance of medical students, junior doctors, residents, and senior clinicians, this research aims to identify areas of strength and improvement as well as to explore the educational implications for improving training curricula in radiology and clinical diagnostics.

This research contributes to a better understanding of training needs at various levels of medical education, highlighting the importance of targeted interventions and continuing education to improve the overall quality of CXR interpretation in clinical practice. Ultimately, the findings may provide evidence for enhancing medical education programs and improving patient Despite the pivotal role of CXR interpretation in diagnosing conditions such as care outcomes through more accurate and consistent diagnostic practices.

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MATERIALS AND METHODS

Study population

This was a cross-sectional study conducted using CXRs, which were displayed digitally. The inclusion criteria were house officers, medical officers and registrars who were in specialty training. Radiology trainees were excluded from this study. Radiology trainees were excluded from this study because they received formal and focused training in radiograph interpretation, which would give them significantly greater baseline competence than would general medical officers or other non-radiologist doctors. Furthermore, this study aimed to assess competency among doctors with varying levels of general clinical experience. Radiology trainees are not a fair comparator group because of their specialized training.

The sample size calculation is based on a confidence level of 95%, a confidence interval of 5%, and a margin of error of 5% with a standard deviation (SD) of 0.5. The ideal sample size on the basis of the calculation is 278 participants.

A total of 309 participants were recruited however four were excluded because of incomplete data, resulting in a final number of participants of 305.

Methods

Participants were recruited on the basis of voluntary participation. To minimize selection bias, we recruited participants from multiple facilities, which included participants from tertiary hospitals, district hospitals, and university settings as well as from health clinics in Kuching and Samarahan Divisions.

Researchers approached each of the participants individually and were present to observe and ensure that the participants completed the questionnaire independently, without external assistance or influence.

The participants were requested to provide their demographic data, years of service, and current postings. A standard set of ten radiographs was chosen. The number of CXRs used to assess the participants was adapted from previous studies and ranged from seven to ten.[1,2,3,4] This number was considered sufficient to evaluate key interpretation skills while minimizing participant fatigue and maintaining focus during the assessment.

The following standards were utilized in the selection of the study's images: (i) only one primary diagnosis on the radiograph with no secondary abnormalities, (ii) two radiologists with more than 10 years of experience independently verified the primary diagnosis, (iii) the findings of the primary diagnosis were clear and not obscured by any structures and (iv) no artifacts were detected.

The final selected CXRs were normal CXR, clavicle/rib fracture, lung mass, metastatic lung lesions, congestive heart failure, pneumomediastinum, pneumothorax, pneumoperitoneum, pulmonary tuberculosis, and lung collapse. The images were exported in JPEG format to maintain the original image quality.

For each image, the participants selected a single primary diagnosis in a multiple-choice format with ten choices given. We choose a multiple-choice question format over free-text responses mainly for standardization purpose as to ensure that all participants are assessed with the same options, thus reducing the variability in the responses and increasing the objectivity of the evaluation. It is also easier to mark consistently, especially in our study with a relatively large sample size, as this approach can minimize scoring bias. In free-text, participants might have the correct idea but are unable to express it clearly. Multiple-choice formats reduce such issues by offering clear choices. Above all, responses from multiple-choice formats are easier to analyze statistically, enabling more accurate comparisons and conclusions.

The participants also documented their confidence level concerning their chosen diagnosis. The confidence level of the participants in interpreting CXR was assessed via a self-reported Likert scale. For each of the 10 radiographs, participants rated their confidence on a scale from 1 (totally not confident) to 5 (highly confident). Each radiograph contributed a maximum of 5 points, resulting in a total possible confidence score of 50. This cumulative score reflected the overall self-perceived confidence of each participant in interpreting CXRs. For the purpose of analysis, the responses were recategorized into three levels: not confident (scores ranging from10-20 points), moderately confident (scores ranging from 21-39 points) and highly confident (scores ranging from 40-50 points). This transformation resulted in categorical variables to facilitate group comparisons in the analysis via Chi-square tests to assess associations with other variables.

Two phases were carried out. In Phase 1, the participants will be given CXR without a clinical history, and in Phase 2, a similar CXR will be given: however they will have an additional clinical history. For each CXR, a single-sentence clinical history was provided to simulate real-world scenarios. The clinical histories were formulated and reviewed by a panel of five consultant radiologists. Among them, three were part of the research team, while two were independent radiologists who were blinded to the final diagnosis and study outcomes to reduce bias. This review process ensured that the clinical history was concise, relevant, and free from leading information that might influence interpretation.

Data analysis was performed via IBM SPSS Statistics software, version 25. Descriptive statistics were used to summarize the demographic data. Categorical variables are presented as frequencies and percentages, and were compared via the Chi-square test. A P-value of < 0.05 was considered statistically significant. All analyses were conducted at the 95% confidence level.

RESULTS

A total of 305 participants were included in this study. The overview of the participants' information and interest is summarized in Table I. The number of correct diagnoses for each participant is summarized in Figure I.

Table I: Demographic & Basic Data of Participants (n=305)

	n (%)
Gender	
Male	117 (38.4)
Female	188 (61.6)
Current level of service	
House Officer	76 (24.9)
Junior Medical Officer (<3 years)	98 (32.1)
Senior Medical Officer (>3 years)	102 (33.4)
Medical Officer in specialty training	29 (9.5)
Graduated from	
Local Public University	134 (43.9)
Oversea/Private University	171 (56.1)
Radiology posting during undergraduate studies	
Yes	138 (45.2)
No	167 (54.8)

Table II: Association between the ability to interpret CXR with presence and absence of clinical history

		With history			
Without history		High score	Medium score	Low score	Total
	High score	73	26	11	110
	Medium score	29	30	36	95
	Low score	9	27	64	100
Total		111	83	111	305

Pearson Chi-square value (p-value): 91.906 (p<0.001)

Table III: Chi square test for factors affecting the total scores for CXR without and with history given

	Low Score, n		Moderate score, n		High score, n		Pearson Chi-Square Value (p-value)	
	w/o hx	hx	w/o hx	hx	w/o hx	hx	w/o hx	hx
Gender								
Male	29	34	40	37	48	46	5.564	4.608
Female	71	77	55	46	62	65	(0.062)	(0.100)
Current level of training								
House Officer	31	37	22	20	23	19	10.803	12.222
Junior Medical Officer (<3years)	39	37	26	29	33	32	(0.095)	(0.057)
Senior Medical Officer (>3years)	22	29	37	26	43	47		
Medical Officer in specialty training	8	8	10	8	11	13		
Field of interest								
Medical	15	17	12	10	23	23	17.873	12.826
Surgical	19	20	12	17	15	9	(0.022)	(0.118)
Community/Public Health	19	24	20	19	37	33		
Radiologist	1	3	3	0	0	1		
Undecided	46	47	48	37	35	45		
Graduated from								
Local Public University	48	50	45	39	41	45	3.108	0.889
Oversea/Private University	52	61	50	44	69	66	(0.211)	(0.641)
Radiology Posting in Undergraduate Training								
Yes	47	58	49	39	42	41	3.878	5.394
No	68	53	46	44	53	70	(0.144)	(0.067)
Confidence level when answering								
Not confident	15	16	6	8	7	4	18.399	14.636
Moderate	65	70	85	52	55	61	(0.001)	(0.006)
Confident	20	25	26	23	48	46		

*w/o hx = without history given, hx= with history given

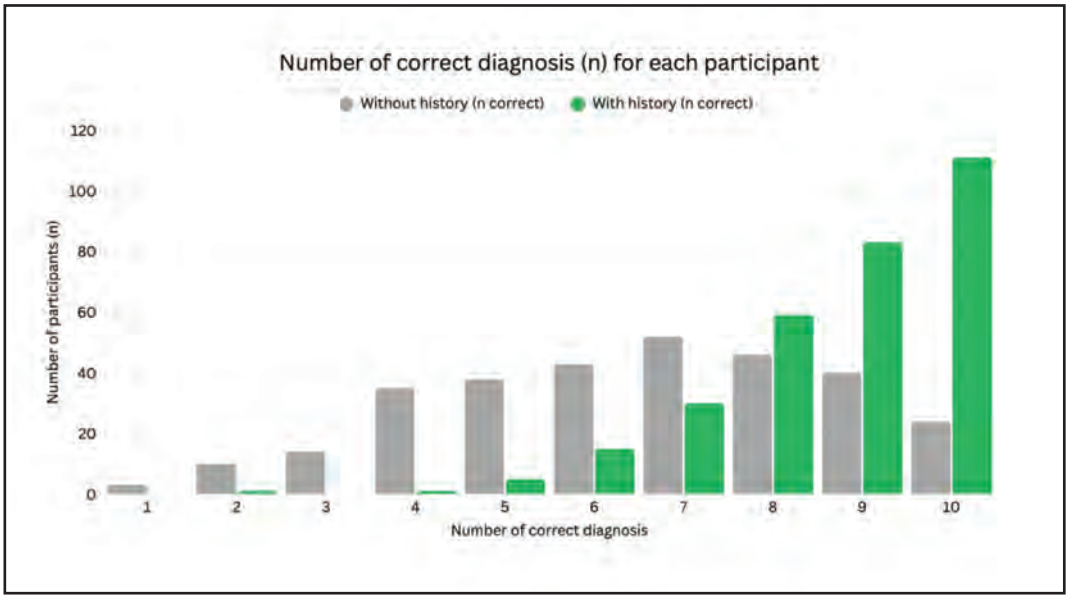

Fig. 1: Bar chart showing number of correct diagnosis for each participant

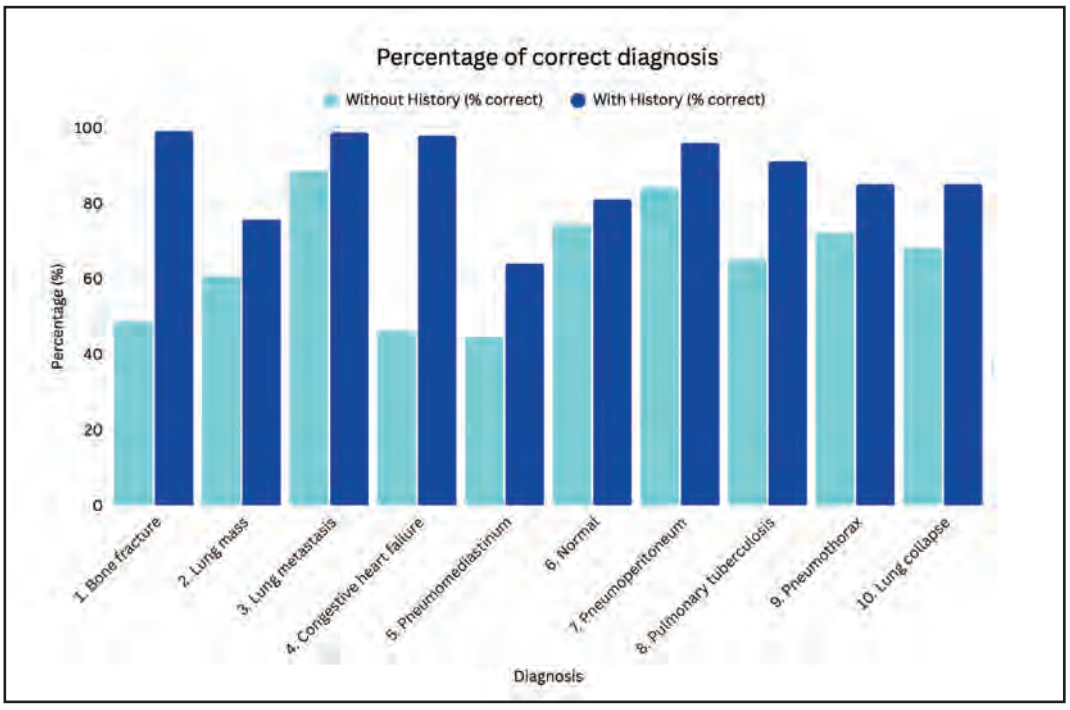

Fig. 2: Bar chart showing percentage of correct diagnosis for each image

The percentage of participants whose CXRs were accurately interpreted improved when clinical history was given; from 7.9% of participants who achieved perfect scores without clinical history to 36.4% of participants who achieved perfect scores with clinical history. Figure I shows a bar chart showing the number of correctly interpreted CXRs for each participant. The chi-square test revealed a statistically significant correlation between the accuracy of CXR interpretation and the presence or absence of a clinical history, as shown in Table II. Patient history during CXR interpretation is significantly related to higher CXR interpretation accuracy scores.

The median score for correctly interpreted CXRs without history was 7.0 out of 10.0, and the median score for correctly interpreted CXRs with history was higher, with a score of 9.0 out of 10.0. The participants were divided into high scorers for those who scored at and above the 75th percentile, which was 8.0 out of 10.0 and low scorers for those who scored at the 25th percentile and below, which was 5.0 out of 10.0 for those without history. For the CXRs with accompanying clinical history, the high score was for those who were at the 75th percentile and above, which was a full score of 10.0 out of 10.0, and the low score was at the 25th percentile and below, which was a score of 8.0 and below.

The percentage of correct diagnoses for each image is summarized in Figure II. Without a clinical history, the majority of the participants could accurately identify CXRs with lung metastasis (88.5%) and pneumoperitoneum (84.2%). The image with the least number of accurate answers is pneumomediastinum.

The chi-square test was performed to analyze the factors affecting the total scores of the participants. The factors that were included as variables include gender, the level of training or years of experience, their field of interest, their undergraduate universities whether from local or overseas universities, whether there is a radiology posting in their undergraduate studies, and their confidence level when interpreting CXRs. Generally, the field of interest and confidence level when reporting a CXR without history were associated with greater accuracy when interpreting a CXR. The results are summarized in Table III. However, if the clinical history was given to the participant, only the confidence level of the participant affected the final score of the CXR interpretation.

The mean confidence level when reporting a CXR increased from 37.05 +/-6.814 with no history to 42.93 +/-6.024 with a given history.

DISCUSSION

CXR is one of the most widely utilized imaging modalities in clinical practice because of its accessibility, affordability, and diagnostic utility. Proficiency in interpreting CXR is crucial for health practitioners to ensure prompt and precise diagnosis, especially in emergency, respiratory, and cardiovascular disorders.

A lack of proficiency in interpreting CXR could result in incorrect diagnosis, which can lead to delayed treatment; jeopardizing patient safety. Thus, it is essential to incorporate systemic radiology interpretation classes early in medical school and reinforce them during clinical rotations.

Among the 305 participants in our study, the majority (54.8%) did not have a formal radiology posting during their undergraduate years. Their radiograph interpretation skills are derived mainly from the incorporation of radiograph interpretation from other major postings. Several studies have concluded that those with formal training in radiology early in their medical school course have greater competency in interpreting CXRs. [3,5,6] However, our study showed that the ability to interpret a CXR successfully is independent of whether there is a formal radiology posting in their undergraduate years. Most undergraduate radiology postings are short, observational, and lack hands-on interpretation experience. Without regular practice, students may be unable to develop the skills needed to accurately interpret CXRs. Furthermore, even if the students have radiology exposure during their undergraduate years, their skills will decline over time without reinforcement. By the time they are practicing, especially if they are not regularly involved in radiology, their retained knowledge may be minimal.

Interpreting CXR without any clinical information poses a notable challenge for clinicians. However, this is one of the many challenges faced by clinicians, especially in emergency settings. Our study revealed a significant increase in the ability to accurately interpret CXR if a patient's clinical history was given, as shown in Figure I and Table II. This is in tandem with all the major studies performed before, and it stresses that understanding the patient's symptoms, medical history, and clinical presentation is crucial and essential for guiding an accurate diagnosis. This finding shows that while chest radiographs can reveal important pathology on their own, interpretation is significantly more accurate and precise when coupled with the patient's clinical history. We therefore stress again the importance of proper clinical information given to any clinician when they are interpreting a CXR, which can eventually lead to better accuracy, fewer errors, and safer decisions when interpreting a CXR. Current radiologic training should highlight both technical reading skills and the importance of incorporating clinical information for the best outcome.

Our study revealed that, with respect to a patient's clinical history, the ability of any clinician to interpret CXR accurately is independent of gender, working experience, field of interest, which university the clinician graduated from, and whether the clinician had a formal radiology posting in their undergraduate studies.

The independence of CXR interpretation skills from different levels of work experience may seem unexpected, but this phenomenon has been echoed in several international studies.[7,8] One of the suggested reasons is due to inadequate radiology exposure during their undergraduate training. Most of the medical curricula provide limited structured exposure to radiology, particularly CXR interpretation. Another possible explanation for why clinical experience does not guarantee interpretation skill is that clinical exposure may only increase familiarity with disease patterns; however, it does not necessarily equate to improved image interpretation unless there is formal feedback and guided training. Studies have shown that feedback is a crucial element in improving educational programs in radiology.[9] However, several studies have shown improved overall median scores with increased level of training.[1,7,10]

This study also does not show a significant difference in the total scores between those who graduated from the local public or from overseas/private universities. In contrast, one of the studies in Jordan showed that the successful interpretation of CXR is closely related to the universities from which they graduated, which is mostly attributed to the curricula of the radiology postings at each of their respective universities.[3]

The confidence level plays a vital role in the accuracy of CXR interpretation, as proven in this study. Our study revealed that higher self-reported confidence is associated with greater diagnostic accuracy. Confident practitioners are more decisive and less likely to second-guess correct interpretations. A higher confidence level comes from greater experience and familiarity with radiological patterns as well as stronger visual recognition skills.[11] The confidence level is the only

common factor that affects the accuracy of CXR interpretation in both circumstances, with and without the patient's clinical history. Studies have indicated that both regular exposure to CXRs and systematic training have positive effects on the confidence level of a clinician when interpreting a CXR.[12,13] Additionally, there is a positive correlation between students' self-confidence levels and their interest in learning.[14] Moreover, self-confidence emerged as a strong predictor of learning interest which underscores the importance of self-confidence among students to increase their learning interest and overall academic engagement.[14] Our findings, supported by global studies, highlight the need for educational strategies that can increase confidence through structured exposure and feedback which can ultimately improve diagnostic accuracy in interpreting CXR.

Interestingly, the accuracy of the interpretation of pneumomediastinum was low despite the patient's clinical history. The diagnosis of pneumomediastinum can be made with CXR in 70-90% of cases[15,16,17], with computed tomography (CT) scans being more definitive in the diagnosis. However, the accuracy varies depending on the quality of the radiograph and the interpreter's experience. A study assessing the competency of family medicine residents in interpreting CXR revealed that only 48.5% correctly identified pneumomediastinum cases.18 Consistent with this finding, our study also demonstrated near similar results with 44.4% of participants accurately diagnosed with pneumomediastinum without a clinical history and which slightly improved with added history to 64.3% accuracy. The lower diagnostic accuracy for pneumomediastinum may be attributed to its rarity in clinical practice, which leads to less exposure and limited familiarity among clinicians, especially non-radiologists. Additionally, pneumomediastinum presents with subtle radiographic signs, which can be easily overlooked on CXR.

The skill of CXR interpretation remains crucial despite the rise of artificial intelligence (AI), as AI can detect patterns, but lacks a the clinical context, whereas clinicians interpret CXR by integrating patient history, physical findings and laboratory results.[19] In addition, the performance of AI might vary with image quality or uncommon cases. On top of that, especially in our country, some hospitals, especially those in rural or lower resource areas, the AI tools are not easily assessable. We strongly believe that AI enhances, but does not replace, the skill of chest X-ray interpretation. A well-trained clinician can apply human reasoning, clinical insight, and ethical judgment, all of which are critical for safe, accurate patient care.

This study is most likely the first study of CXR interpretation in Malaysia involving a variety of doctors working in different fields and with different working experiences. Most importantly, the significance of clinical history in medical practice, particularly in CXR interpretation, was explicitly confirmed by this study's comparison of participant performance in two distinct circumstances in which the clinical history was initially withheld and subsequently given to the participants.

This small-scale study has several limitations despite the significance of the study. First, each diagnosis may present with a range of clinical manifestations on CXR. The ability of the participants to accurately recognize the radiographic pattern in this study does not reflect the ability of the participants to recognize the different manifestations of a similar disease. Second, the gold standard used in our study can also be questioned. Research has demonstrated that even seasoned radiologists may read a CXR differently.[20] However, to minimize this effect, our study recruited two experienced radiologists, and both needed to have a complete consensus on all of our CXRs. Third, the use of voluntary sampling introduces several limitations, as those who volunteer may have a particular interest or confidence in CXR interpretation, which may not represent the general population of doctors. This may lead to an overestimation of competence. Furthermore, voluntary participation leads to an imbalance in the number of participants across different training levels, affecting the statistical power of comparisons. Future studies should consider stratified sampling to better represent the target population and reduce bias.

CONCLUSION

Assessing healthcare professionals' CXR interpretation skills is essential for assessing their readiness to face their daily workloads. However, there is a paucity of literature regarding their ability to interpret CXR. Therefore, this study was carried out to look at the degree of competency among doctors in interpreting CXR and also to explore the best teaching strategy that could support curriculum improvement.

The confidence level plays a vital role in the accuracy of CXR interpretation; thus, we conclude that the key to accurately interpreting a CXR depends heavily on continuous learning and constant practice, as these are essential elements in building higher confidence levels when interpreting CXR. Structured teaching, continuous practice, feedback and integration into clinical decision-making are the keys that translate to greater competency in CXR interpretation. Future researches should emphasize on multicenter approach as it enhances the generalizability of findings to a broader national context. We recommend curriculum reforms or standardized training modules to address this skill gap.

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ETHICS

Ethical approval was provided by the Ethics Committee, Faculty Medicine and Health Sciences, Universiti Malaysia Sarawak UNIMAS (Rujukan Etika: FME/24/127 dated 23 February 2024) and the National Medical Research Register (NMRR ID-23-03359-TZZ).

CONFLICT OF INTEREST

None.

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Evaluating the efficiency of one stop crisis centres in managing domestic violence cases

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ABSTRACT

Introduction: As domestic violence (DV) poses a critical threat to public health worldwide, this prompts the need for efficient and effective intervention. In Malaysia, although One Stop Crisis Centres (OSCCs) have been offering multisectoral services to DV victims for many decades, an evaluation of the efficiency of these centres has yet to be conducted. This study aimed to assess the efficiency and effectiveness of three Malaysian OSCCs using a two-stage Data Envelopment Analysis (DEA) approach.

Materials and Methods: A total of 153 adult DV victims were recruited from OSCCs in Sarawak General Hospital, Universiti Malaya Medical Centre, and Hospital Universiti Sains Malaysia. The inputs included the number of doctors, nurses, and other personnel whereas the outputs were total response time and service quality, measured via a validated 35-item OSCC-Qual instrument. Stage 1 employed an input-oriented Banker, Charnes, and Cooper (BCC) DEA model to determine how efficiently OSCCs managed resources to minimize response times. Stage 2 used an output-oriented BCC model to evaluate the centre's ability to maximize service quality.

Results: The social workers unit recorded notably long mean response times across three centres. Correlation analysis revealed a strong negative association between the number of personnel and the multisectoral coordination dimension of service quality. While most units showed high pure technical efficiency in the input-oriented DEA, scale inefficiencies were shown to be common in all centres. Pure technical efficiency measures how well resources are utilized regardless of scale, whereas scale efficiency assesses whether an organization operates at its optimal size (neither too large nor too small). In the output-oriented model, all centres similarly demonstrated good pure technical efficiency but continued to grapple with scale inefficiencies, especially at Sarawak General Hospital and Hospital Universiti Sains Malaysia.

Conclusion: These findings highlight the importance of optimizing operational scale in OSCCs. Tailoring resource allocation and strengthening coordination among multidisciplinary teams could reduce response times and improve care for DV victims.

KEYWORDS:
Efficiency; effectiveness; domestic violence; OSCC; Malaysia

INTRODUCTION

Domestic violence (DV) is a pervasive global public health issue with significant threats to the well-being and safety of its victims.[1] Globally, 1 in 3 women have experienced some form of physical or sexual intimate partner violence or non-partner sexual violence in their lifetime.[2] The Coronavirus Disease 2019 (COVID-19) pandemic had further exacerbated this problem, leading to a rise in the number of cases.[3] Victims often endure physical injuries, emotional trauma, and sexual health issues, including depression, anxiety, unintended pregnancies, and sexually transmitted infections like HIV.[2,4,5] In Malaysia, domestic violence cases are managed through One Stop Crisis Centres (OSCCs), located in all Emergency and Trauma Departments (ETDs) of Ministry of Health hospitals, which provide integrated multiagency services to victims of DV, sexual assault, child abuse, and neglect.[6]

Despite their critical role, no systematic evaluation of OSCC efficiency and effectiveness has been conducted, leaving important knowledge gaps on human resource utilization, service quality, and outcomes in terms of timeliness of response in these centres in Malaysia. Broadly, efficiency refers to a centre's ability to achieve a specific response time using minimal healthcare resources while maintaining service quality standards, whereas effectiveness is defined as the extent to which level of service quality achieved aligns with the organization's goals.[7-9] Measuring both efficiency (timely operations) and effectiveness (quality services) is crucial for OSCCs, as improved efficiency can enhance management, leading to more effective and sustainable care for DV victims. Hence, this study aimed to investigate the efficiency and effectiveness of selected OSCCs in Malaysia using the Data Envelopment Analysis (DEA) method.

MATERIALS AND METHODS

The non-parametric DEA method evaluated the relative efficiency of different decision-making units (DMUs), represented by the OSCCs in this study, by converting inputs (e.g., resources such as staff and time) into outputs (e.g., service quality and response times).

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Participants
A total of 153 adult domestic violence (DV) victims, aged 18 years and above, who received treatment at three selected OSCCs in Malaysia, i.e., in Sarawak General Hospital (SGH), in Universiti Malaya Medical Centre (UMMC), and in Hospital Universiti Sains Malaysia (HUSM), were consecutively recruited. Victims who were physiologically unstable at the time of recruitment, or who required immediate treatment, were excluded.

Materials
The input and output variables were collected based on data from OSCC records in these 3 centres except for service quality variable. In this regard, service quality was evaluated by the DV victim using the validated OSCC-Qual instrument[10], a 35-item tool that measures seven key dimensions of service quality on a five-point Likert scale (1 = strongly disagree to 5 = strongly agree). These 7 key dimensions are: (1) supportive environment, (2) multisectoral coordination, (3) tangibles, (4) professionalism, (5) information provision, (6) competency of staff and (7) attitude of staff.10 The OSCC-Qual instrument was scored separately for each of its seven domains for domain-level analyses of the service quality, with no composite total score calculated.[10]

The input variables of this study were:
- I1: Number of doctors
- I2: Number of nurses
- I3: Number of other personnel (e.g., social workers and police).

The output variables of this study were:
- O1: Total response time (undesirable output, treated as input in some models).
- O2: Service quality, measured using the OSCC-Qual instrument.[10]

Procedure
When a DV victim was admitted to an OSCC and received initial treatment, the attending nurse notified the investigators or their research assistants to initiate data collection. After obtaining informed consent, participants were invited to complete the self-administered OSCC-Qual instrument to assess service quality perceptions. The other input and output data were extracted from OSCC records. The study received ethical approval from the Malaysian Medical Research and Ethics Committee (NMRR-20-1437-54831) prior to commencement of the study.

Specifically, in this study, a widely used variant of DEA, i.e., the Banker, Charnes, and Cooper (BCC) model of DEA, was used as this model allows for the assessment of both technical and scale efficiency, while accommodates for the variations in resource utilization and operational capacity across different DMUs.[11]

Based on Seiford and Zhu's method[12], a two-stage DEA model was conducted where the output (O1) generated based on the inputs (I1, I2 and I3) in the first stage would subsequently become the input of the second stage to generate its output (O2). Therefore, Stage 1 is an input-oriented BCC DEA model to evaluate organization's efficiency in converting inputs into fixed response times, while Stage 2 is an output-oriented BCC DEA model to evaluate the effectiveness of OSCCs in meeting service quality expectations. In this study, although the output O1 in the first stage can be considered as an "undesirable output" (as longer response time means less efficient), it can be treated as an input in performing DEA as shown by lo Storto and Goncharuk.[13] Integrating these models provided a comprehensive perspective on the efficiency of OSCC operations and outcomes, enabling an independent evaluation of input utilization and outcome maximization. This dual approach offers valuable insights to guide decision-makers in identifying areas for improvement and optimizing resource allocation.

Data analysis
Descriptive statistics on the characteristics of the OSCCs and spearman rank correlation analysis to determine the relationships between the various input and output variables were performed using the Statistical Package for Social Sciences (SPSS), version 29.0. Data Envelopment Analysis Program (DEAP) version 2.1 (available for free download from https://economics.uq.edu.au/cepa/software) was used to construct the DEA frontiers under variable return to scale according to the Banker, Charnes and Cooper (BCC) models to determine the pure technical efficiency (PTE), scale efficiency (SE) and overall technical efficiency (OTE) [11]. PTE measures how well a production unit converts inputs into outputs, without considering the scale impact. It is a reflection on how well a unit manages its resources. In this regard, PTE refers to the ability of an OSCC to maximize outputs (e.g., service quality) using a given set of inputs (e.g., staff and time). SE, on the other hand, measures how well a unit is operating at its optimal scale. A unit is scale efficient when its size is optimal, where changing its size (i.e., making it larger or smaller) would make it less efficient. In other words, SE evaluates whether inefficiencies arise from operations being too large or too small relative to their optimal scale. In this regard, SE describes the capacity of OSCCs to operate at an optimal size or capacity. On the other hand, OTE describes the relationship between SE and PTE where SE is the ratio of the OTE score to the PTE score (SE = OTE/PTE) or OTE = SE x PTE. [14]

RESULTS

Table I shows that the observed response times varied widely across the three OSCCs. The social workers unit shows the longest response times at all three centres, particularly in SGH, where the mean response time was 1018.8 minutes and the median was 435.0 minutes. The police unit response times are relatively consistent across the three centres, with all showing a median response time of 60 minutes. Within the specific individual centres, SGH generally had lower response times across most units when viewed alongside the other two centres. However, the social workers unit stands out as a significant outlier, with an extremely high mean response time.

Variations were observed in service quality scores across the three OSCC centres, with HUSM apparently receiving the highest overall scores, as well as in the dimensions of

Table I: Observed Response Time Across Three OSCC Centres

Response Time (in minutes)	SGH			UMMC			HUSM		
	Cases	Mean	Median	Cases	Mean	Median	Cases	Mean	Median
Emergency and Trauma Unit	46	27.3	12.0	51	101.3	30.0	51	35.0	25.0
Radiology Unit	-	-	-	-			2	30.0	30.0
Psychiatry Unit	-	-	-	3	65.0	60.0	50	70.5	50.0
Obstetrics and gynaecology Unit	5	69.0	60.0	7	51.0	51.0	2	297.5	297.5
Ear, Nose and Throat Unit	2	25.0	25.0	1	180.0	180.0	3	35.0	30.0
Surgery Unit	-	-	-	-	-	-	2	17.5	17.5
Cardiothoracic Unit	-	-	-	-	-	-	1	35.0	35.0
Orthopedics Unit	-	-	-	-	-	-	5	37.0	45.0
Ophthalmology Unit	4	68.8	47.0	-	-	-	10	57.5	52.5
Oral and Facial Care Unit	2	125.0	125.0	-	-	-	-	-	-
Social Workers Unit	15	1018.8	435.0	6	122.5	120.0	51	113.2	100.0
Police Unit	25	70.4	60.0	50	60.0	60.0	29	60.0	60.0

Table II: Observed Service Quality Scores Across Three OSCC Centres

Service Quality (in scores)	SGH		UMMC		HUSM	
	Mean	Median	Mean	Median	Mean	Median
Supportive Environment	4.3	4.2	4.0	4.0	4.6	5.0
Multisectorial Coordination	4.2	4.0	3.3	3.0	4.4	4.3
Tangibles	3.5	3.7	3.2	3.3	3.8	3.3
Professionalism	4.4	4.6	4.2	4.3	4.6	4.8
Information Provision	4.2	4.2	4.0	4.0	4.3	4.4
Competency of Staff	4.4	4.6	4.3	4.1	4.5	4.4
Attitude of Staff	3.4	3.3	3.3	3.3	3.5	3.3
Overall Rating	4.4	5.0	4.2	4.0	4.5	4.0
Overall Service Quality	4.2	4.2	3.9	3.9	4.1	4.1

Table III: Result of Spearman rank correlation analysis

Variables	ETD Units				Referral Units			
	Number of personnels		Total Response Time		Number of personnels		Total Response Time	
	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value
Supporting Environment	-0.005	0.953	-0.138	0.090	0.215	0.008*	0.207	0.010*
Multisectorial Coordination	-0.410	0.001*	-0.209	0.009*	-0.605	0.001*	-0.483	0.001*
Tangibles	0.037	0.650	0.019	0.820	0.038	0.645	0.022	0.788
Professionalism	-0.104	0.201	-0.089	0.272	0.156	0.054	0.136	0.092
Information Provision	-0.095	0.244	-0.057	0.481	0.085	0.295	0.068	0.403
Competency of Staff	-0.078	0.341	-0.033	0.685	0.070	0.387	0.060	0.462
Attitude of Staff	0.096	0.237	-0.131	0.105	0.175	0.030*	0.159	0.050*
Service Quality	-0.133	0.101	-0.113	0.166	-0.003	0.971	0.010	0.898

Notes: Asterisk (*) denotes 5% level of significance. All analyses were conducted using Spearman rank correlation.

Table IV: Integrated Performance Measures for Input-Oriented BCC DEA Model

Units	Input-Oriented BCC DEA Model								
	Overall Technical Efficiency			Pure Technical Efficiency			Scale Efficiency		
	SGH	UMMC	HUSM	SGH	UMMC	HUSM	SGH	UMMC	HUSM
Emergency and Trauma Unit	0.180	0.563	0.102	1.000	1.000	0.365	0.180	0.563	0.279
Radiology Unit	-	-	0.101	-	-	0.522	-	-	0.193
Psychiatry Unit	-	0.362	0.237	-	0.429	1.000	-	0.842	0.237
Obstetrics and gynaecology Unit	0.394	0.298	1.000	1.000	0.674	1.000	0.394	0.442	1.000
Ear, Nose and Throat Unit	0.200	1.000	0.118	1.000	1.000	0.375	0.200	1.000	0.314
Surgery Unit	-	-	0.024	-	-	0.200	-	-	0.118
Cardiothoracic Unit	-	-	0.118	-	-	1.000	-	-	0.118
Orthopedics Unit	-	-	0.124	-	-	0.254	-	-	0.490
Ophthalmology Unit	0.550	-	0.193	0.829	-	0.197	0.664	-	0.984
Oral and Facial Care Unit	1.000	-	-	1.000	-	-	1.000	-	-
Social Workers Unit	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Police Unit	0.069	0.490	0.530	0.600	1.000	1.000	0.115	0.490	0.530
Median score	39.4	52.7	12.4	100.0	100.0	52.2	39.4	70.3	31.4

Table V: Integrated Performance Measures for Output-Oriented BCC DEA Model

	OUTPUT-ORIENTED BCC DEA MODEL		
Centres	**Overall Technical Efficiency**	**Pure Technical Efficiency**	**Scale Efficiency**
SGH	0.533	0.988	0.539
UMMC	1.000	1.000	1.000
HUSM	0.719	1.000	0.719
Median score	71.9	100.0	71.9

supportive environment for victims, multisectoral coordination, tangibles, staff attitude, professionalism, and competency of staff (Table II).

Spearman's rank-order correlation analysis

Spearman's rank-order correlation analysis was performed to determine the correlations between the number of personnel, total response times in ETD units and referral units, and service quality across seven domains (Table III).

The analysis revealed a strong negative correlation between the multisectoral coordination domain of service quality and the number of personnel in ETD units ($r = - 0.410$, $p = 0.001$) and referral units ($r = - 0.605$, $p = 0.001$), as well as total response time in referral units ($r = - 0.483$, $p = 0.001$). Additionally, a weak negative correlation was also observed between multisectoral coordination and total response time in ETD units ($r = - 0.209$, $p = 0.009$).

On the other hand, the supporting environment domain of service quality showed a significant positive correlation with the number of personnel in referral units ($r = 0.215$, $p = 0.008$) and total response time ($r = 0.207$, $p = 0.010$). Additionally, the attitude of staff also showed a significant positive correlation with the number of personnel in referral units ($r = 0.175$, $p = 0.030$) and with total response time ($r = 0.159$, $p = 0.050$). Other service quality dimensions, including tangibles, professionalism, and competency of staff, did not exhibit significant correlations with the number of personnel or total response time.

Integrated Input-oriented and Output-oriented BCC DEA models

Stage 1 – Input-oriented BCC DEA model

Stage 1, an input-oriented efficiency model, assessed the potential for reducing input quantities while maintaining output levels. Table IV shows that most units in all three centres achieved a PTE score of 1.000 but significant scale inefficiencies are evident across various units, as evidenced by SE values below 1.000. Specifically, for Emergency and Trauma unit, SGH and HUSM exhibited poor OTE scores (0.180 and 0.102), while UMMC performed relatively better (0.563) but scale inefficiencies are evident across all 3 centres. For Obstetrics and Gynaecology Unit, although SGH and UMMC achieved full PTE (1.000), but at the same time, these 2 centres also showed scale inefficiencies with SE of 0.394 and 0.442 respectively. For Radiology, Psychiatry and Police units, these units show consistently low OTE and SE scores across all centres.

Stage 2 – Output-oriented BCC DEA model

Both UMMC and HUSM have perfect PTE score of 1.000, although only UMMC achieves an OTE score of 1.000. Although SGH also had a close to perfect PTE score of 0.988, it had the lowest OTE score of 0.533 due to scale inefficiency with SE of only 0.539 (Table V).

DISCUSSION

The response times (both mean and median) vary significantly across the three centres, suggesting differences in operational efficiency or resource availability. Most prominently, the Social Workers Unit shows the longest response times at all three centres, especially in SGH, where the mean response time is 1018.8 minutes, and the median is 435.0 minutes. While the long response times in the Social Workers Unit may initially seem inefficient, they may also reflect the critical and multifaceted role of social workers in addressing the safety, legal, and emotional needs of domestic violence victims. For example, social workers are often responsible for arranging safe and undisclosed temporary shelters for DV victims in order to shield them from further violence, stigmatization, and secondary traumatization.[15,16] This process requires meticulous coordination to ensure the victim's safety and well-being. Additionally, legal processes such as obtaining Emergency Protection Orders (EPOs) or Interim Protection Orders (IPOs) often necessitate extended response times due to the involvement of police and judicial authorities.[6] Further complexity can also arise when victims have young children or babies accompanying them, as social workers must address the needs of both the victim and the child, such as securing essential resources and ensuring emotional support.[17] In this study, for SGH OSCC, the Social Workers Unit data show a mean of 1018.8 minutes and a median of 435.0 minutes, suggesting that the data is skewed to the right. This means that there are a small number of very complex cases (outliers) requiring a lot of social welfare support and interventions.

The correlation analysis revealed a strong negative correlation between the multisectoral coordination domain of service quality and the number of personnel in ETD units, the number of referral units as well as the total response time in referral units. This suggests that an increase in personnel does not necessarily improve coordination, which is critical for ensuring timely responses to DV victims. In fact, paradoxically, this is perceived as a decrease in service quality, potentially due to inefficiencies such as communication breakdowns, overlapping and redundant roles, or lack of clear responsibilities between different teams, which require the repeated need for DV victims to retell their traumatic experiences to different healthcare staff. This repetition can lead to secondary traumatization[15,16], further exacerbating the emotional burden on victims and negatively impacting their perception of service quality.

With regards to Stage 1 (input-oriented) BCC DEA analysis, it was found that most units in all three centres achieved a PTE score of 1.000, indicating that they were efficient in managing inputs to produce outputs regardless of scale inefficiencies. But at the same time, there were significant scale inefficiencies across various units in all 3 centres. In other words, the results indicate that scale inefficiency, rather than the technical inefficiency of resource utilization, was a primary contributor to poor overall efficiency (OTE) in most units. Hence, units with scale inefficiencies need to adjust their scale either by increasing or decreasing resource deployment in order to achieve a more optimized SE.

Similarly, in the Stage 2 (Output-Oriented) BCC DEA analysis, all 3 centres demonstrated excellent PTE scores suggesting that these centres were managing resources efficiently. Their inefficiencies were not due to resource mismanagement or operational workflows but rather scale inefficiencies. Scale inefficiency was the primary factor contributing to differences in OTE, particularly for SGH and HUSM. Both centres should explore strategies to reduce their operational scale, such as redistributing resources, managing patient volumes, as well as improving workflow coordination.

This study has a number of pertinent limitations that need be mentioned. First, the assumption of DEA that all DMUs operate under similar conditions may not reflect real-world variations particularly in healthcare settings. Indeed, the non-homogenous nature of DMUs in hospital settings raises concerns about fair evaluation of all DMUs [18]. Unlike in manufacturing and banking settings where standardized goods and services are produced and rendered under more controlled and repeatable processes, healthcare operates in a highly variable environment. For example, each victim or patient is a unique individual with varying levels of disease complexity. They may present with differing severities of trauma, comorbidities, and treatment and psychosocial needs, making it challenging to standardize inputs (resources) and outputs (health outcomes). Furthermore, unlike factories, where outputs are easily measurable (e.g., the number of goods produced per unit time), healthcare outcomes are multidimensional and include both clinical outcomes (e.g., recovery rates, reduced symptoms) and patient satisfaction (e.g., perceived quality of care). These outputs are harder to quantify and standardize. Hence, efficiency scores derived from models like DEA using measures of inputs (e.g., number of staff) and outputs (e.g., response time or service quality) can be rather simplistic and may fail to fully capture the nuanced processes involved in delivering individualized care. For these reasons, whilst longer response times are typically viewed as inefficiencies, this may not always be so in a healthcare setting. Some extended response times could arise be due to the complexity of the case or the legal procedures associated with the case. Another key limitation specific to this study is that only standardized human resources, such as the number of doctors, nurses and other staff, were captured as input without accounting for other critical resources like infrastructures or other organizational factors that characterize each of the 3 OSCCs. The omission of other non-standardized variables lead into incomplete representation of resource utilisations. Another limitation of this study is its focus on only three OSCC were analysed. This may affect the generalizability of the findings and restricted the number of input and output variables used. Future research perhaps should include a larger number of centres and incorporate contextual factors such as staff training, staff experience, and geographical disparities in access to care, as these elements may influence service delivery and patient outcomes in OSCC centres.

CONCLUSION

A two-stage DEA BCC model conducted to evaluate the relative performance of 3 OSCCs revealed some significant scale inefficiencies although all of them achieved high PTE. Therefore, optimising the operational scale is as important as efficient resource management in OSCC. Efforts to address human resource constraints and enhance service quality are essential to ensure that OSCCs will be better utilized and managed as a safe place to meet the needs of DV victims.

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Factors associated with the practice of home blood pressure monitoring among healthcare providers in public healthcare clinics in Putrajaya

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ABSTRACT

Introduction: Hypertension remains a leading global health concern due to its high prevalence and serious health complications. Nowadays, home blood pressure monitoring (HBPM) has emerged as a valuable non-pharmacological intervention to control blood pressure (BP). Numerous studies have demonstrated the pattern of HBPM practice among hypertensive patients. However, information on optimal practice of HBPM instruction by the healthcare providers (HCPs) is still lacking. Therefore, the main objective of this study is to assess the prevalence of optimal practice of HBPM instruction methods by the HCPs to their hypertensive patients and factors associated with it.

Materials and Methods: This is a cross-sectional study, conducted among HCPs with working experience of more than a year, from all four government primary health clinics in Putrajaya between March 2023 and September 2024. The validated Malay-version i-HBPM questionnaire, also known as "the practice of HBPM instruction methods for hypertensive patients" questionnaire was used in this study.

Results: A total of 285 HCPs were recruited in this study. The prevalence of optimal practice of HBPM instruction methods by the HCPs to their hypertensive patients was 14.4%. The most frequently reported barriers to HBPM recognition among HCPs were a lack of understanding of HBPM (28.8%), a lack of HBPM guidelines (17.2%) and the high cost of devices (16.5%). From the HCPs' thought and perspective, the top three most significant patient-related barriers were a lack of understanding of HBPM (42.1%), followed by high device cost (33.0%) and low education level (29.5%). Attending HBPM training was the only significant factor associated with the optimal practice of HBPM instruction methods given by HCPs to their patients (adjusted OR 3.48, 95.0% CI 1.29, 9.34, p = 0.013).

Conclusion: This study demonstrated a low prevalence of optimal practice of HBPM instruction methods provided by HCPs to their hypertensive patients despite high recognition and recommendation of HBPM among HCPs. HBPM training for HCPs is very crucial to improve their knowledge and consultation skills on HBPM.

KEYWORDS:
Home blood pressure monitoring; practice instruction methods; healthcare providers; hypertension management; training HBPM

INTRODUCTION

Hypertension remains a leading global health concern due to its high prevalence and serious health complications leading to cardiovascular and chronic kidney diseases, especially in low- and middle-income countries.[1-3] Despite advancement in treatment, however, rates of blood pressure (BP) control remain suboptimal, with only a small number of patients achieving the target levels, primarily those receiving treatment in the primary care settings. For the past decades, there has been a fluctuating trend in the prevalence of hypertension in many countries around the globe, including Asia. For instance, China has reported an increased prevalence of hypertension among adults from 20.8% in 2004 to 29.6% in 2010, but has declined to 24.7% in 2018, demonstrating good progress in the prevention and control.[4]

While in Malaysia, about 80.0% of hypertensive patients receive treatment in the primary care setting, but only half of them (40.0%) managed to achieve controlled BP, which puts the other half at risk of morbidity and mortality.[5] In terms of disease trend, the prevalence of hypertension slightly decreased from 32.7% in 2011 to 30.3% in 2019 and 29.2% in 2023.[5-7] Compared to other neighbouring countries in Southeast Asia, the prevalence of hypertension in Malaysia is still higher than in Singapore (23.5%), Thailand (24.7%), Indonesia (26.5%), and the Philippines (28.0%).[8]

Home blood pressure monitoring (HBPM) has emerged as a valuable tool to control BP, subsequently improving hypertension outcomes by empowering patients to self-monitor their BP outside the clinic setting (such as home, pharmacy, office, etc.).[9,10] Numerous studies recommend the practice of HBPM among hypertensive patients due to its convenient, cost-effective, user-friendly ability to detect white-coat syndrome (masked hypertension), ability to improve BP control, and ability to adhere the patient with their medication.[8,11,12] However, the effectiveness of HBPM highly depends on the recommendations and quality of instruction given by the healthcare providers (HCPs) regarding proper

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practice of HBPM in terms of BP measurement technique, record of BP, interpretation of BP results, and actions when BP reaches an emergency level.[13,14]

The optimal practice of HBPM instruction methods towards hypertensive patients by HCPs is not easy and challenging. Many studies revealed that not only patients, but HCPs also often have a lack of knowledge about HBPM, leading to incorrect practice of HBPM among the patients.[15-17] The incorrect instruction of HBPM by the HCPs could also make hypertension management less effective.[18] In some situations, despite HCPs being aware of HBPM and its implementation based on standard guidelines, however, only a small proportion recommended and instructed HBPM to their hypertensive patients.[10]

The recommendation and optimal practice of HBPM instruction methods towards hypertensive patients are not limited to the duty of the doctors but also other non-doctor HCPs, in view of the doctors have limited time seeing patients due to a high number of patients during clinic follow-up or hospital admission, commitment to other clinical procedures or surgeries and commitment to administrative works.[19,20] The non-doctors, especially nurses and pharmacists, also play crucial roles in patient education regarding HBPM.[21,22] However, studies worldwide across various specialities and healthcare settings have shown that the practice of instruction of HBPM among physicians, surgeons, general practitioners, pharmacists, and nurses remains inconsistent.[15,18,23,24] Other studies demonstrated that the practice of recommendation and optimal instruction of HBPM towards hypertensive patients was still low among non-doctor HCPs, with about 10.0% and 14.0% prevalence among nurses and pharmacists.[18,23]

Factors such as inadequate HBPM training among HCPs, a lack of familiarity with HBPM guidelines, and time constraints in patient care are significant barriers to delivering effective instruction of HBPM to hypertensive patients.[15,18,25] Addressing these challenges requires commitment from HCPs to familiarise themselves with HBPM guidelines, participate in proper training on HBPM, and improve communication skills when treating patients.[10,26,27]

In Putrajaya, a different situation is seen in this federal territory of Malaysia, where the prevalence of hypertension is increasing over the years, from 24.1% in 2015 to 24.7% in 2019 and to 24.9% in 2023.[5-7] The increase in the disease burden may be influenced by the quality of instruction of HBPM given by HCPs to their hypertensive patients at the primary care setting. Therefore, the main aim of this study is to determine the prevalence of optimal practice of HBPM instruction methods given by HCPs from primary health clinics in Putrajaya and its associated factors.

MATERIALS AND METHODS

Study Design and Populations

This observational cross-sectional study was conducted at the government primary health clinics in the Federal Territory of Putrajaya under the administration of Putrajaya Health Office from March 2023 until September 2024. The study population consisted of different professions of HCPs (i.e., Family Medicine Specialists (FMS), medical officers (MO), medical assistants (MA), pharmacists, and nurses) working more than one year at all primary healthcare clinics of Putrajaya (Presint 9 Health Clinic, Presint 11 Health Clinic, Presint 14 Health Clinic, and Presint 18 Health Clinic).

Sample Size and Sampling Method

The sample size was calculated using a single population proportion formula, considering a 95.0% confidence level, a 5.0% margin of error, a 20.0% buffer for non-response, and the prevalence of instruction of HBPM by HCPs (19.7%),[10] resulting in a minimum required sample size of 296. Due to the limited number of pool populations of 350 HCPs in all primary health clinics in Putrajaya, the Krejcie and Morgan formula 1970 was applied to accommodate and manoeuvre this limitation.28 The new minimum required sample size was 145.

Study Tools

The "instruction practice of HBPM for hypertensive patients" questionnaire, also known as *i-HBPM* in this study, was used in this study to assess the practice of this HBPM instruction by HCPs. It was originally derived from the study done among physicians in Japan.[10] It was then modified and validated to suit the population settings in Asian countries, including Malaysia.[17] Permission to use questions from the original survey was obtained from the authors. In view of one of the group respondents being a public health nurse and the local setting in Putrajaya that mainly uses the Malay language, the questionnaire required a standard forward-backwards translation process by two bilingual subject matter experts, which was done during the pre-validation study.

In the validation study, 30 HCPs (who were different from the main study) were recruited. The Malay version of *i-HBPM* was found to be well-understood and acceptable; therefore, no further modifications were made. The tool's internal consistency was excellent, with a Cronbach's alpha of 0.97, confirming its reliability for use among the target population. The questionnaire is self-administered and consists of four sections: A, B, C, and D. Section A comprises the sociodemographic background of HCPs, such as age, gender, ethnicity, and level of education. Section B comprises a professional practice profile, such as the type of profession and years of practice, status of HBPM training, and the number of hypertensive patients seen.

Section C focuses on the recommendation of HBPM by HCPs to the hypertensive patients, HBPM usage among hypertensive patients, and recognition by HCPs and patients as an efficient non-pharmacological intervention to control BP. Section D focuses on how the HCPs instruct their patients in terms of the seven correct practices of HBPM, with one correct item giving one mark, contributing to a minimum score of zero and a maximum score of seven marks. The scores were then categorised into "optimal instruction practice of HBPM" (full marks) and "non-optimal instruction practice of HBPM" (score of less than seven marks). In the same section, awareness of the HCPs was assessed by asking about the reference value of home BP. Respondents who answered correctly were classified as having "good awareness", and those who did not were classified as having "poor awareness".

Table I: Sociodemographic background and professional practice profiles (N = 285)

Variables	n (%)	Median (IQR)
Sociodemographic background		
Age (Years)		37 (9)
Gender		
Male	52 (18.2)	
Female	233 (81.8)	
Ethnicity		
Malay	240 (84.2)	
Chinese	15 (5.3)	
Indian	21 (7.4)	
Others	9 (3.1)	
Educational Level		
Primary & secondary education	39 (13.7)	
Tertiary education	246 (86.3)	
Professional Practice Profiles		
Type of Profession		
Family Medicine Specialist	9 (3.2)	
Medical Officers	91 (31.9)	
Pharmacists	39 (13.7)	
Medical Assistants	64 (22.5)	
Staff Nurse	42 (14.7)	
Public Health Nurse	40 (14.0)	
Duration of practice (Years)		8 (7)
Attended HBPM training		
Yes	195 (68.4)	
No	90 (31.6)	
Interaction with hypertensive patients (%)		45.0 (47.5)

Data collection

A simple random sampling method was applied at the beginning of the study by selecting the respondents from the available name list of HCPs from each government primary health clinic in Putrajaya. A computer-generated random number list (using the RAND function in Microsoft Excel) was used to select names for study invitation. The selected names were then screened based on the criteria in the preliminary questions given through each clinic representative via *WhatsApp* link. The inclusion criteria were a Malaysian citizen, HCPs of MOH Malaysia, working for more than a year in the primary health clinic, having a valid practising certificate, and being able to read in Malay or English. Those who were eligible to participate in the study were informed by the researcher. Subsequently, they received a *WhatsApp* link to the written consent that was attached to the questionnaire. Those who agreed to participate proceeded to the questionnaire. Those who disagreed skipped the questionnaire. The on-site researchers were available at the primary health clinic and by phone to assist the respondents. Two reminder text messages were sent each week for three weeks to the clinic representatives.

Data analysis

The data was generated automatically in the Microsoft Excel document once the respondents completed the questionnaire. This data was transferred to the IBM Statistical Package for Social Sciences (SPSS) version 29 for statistical analysis. There was no missing information, misinformation, or duplication of data since the online questionnaire was previously set with these safety features. Continuous data was checked for data distribution. Normally distributed continuous data were presented as mean and standard deviation (SD), and non-normal data distribution was presented as median and interquartile range (IQR). The categorical data were presented in numbers and percentages.

Logistic regression analysis was performed to determine the associated factors of the practice of optimal instruction of HBPM among the HCPs. All variables with a p-value < 0.25 in the simple logistic regression (SLR) analysis were included in the multiple logistic regression (MLR) analysis. The likelihood of practising optimal instruction of HBPM in the SLR and MLR analysis was presented as crude odds ratio ($_{\text{crude}}$ OR) and adjusted odds ratio ($_{\text{adjusted}}$ OR), respectively. A p-value < 0.05 was considered statistically significant.

Ethical Approval

This study was registered under the National Medical Research Registry (NMRR), Ministry of Health (MOH) Malaysia, with an ID of NMRR-23-03068-33X (IIR). Before the commencement of the study, ethical clearance was obtained from the Malaysian Medical Research and Ethics Committee (MREC), MOH Malaysia. Approval to carry out this study was obtained from the Putrajaya Health Office.

RESULTS

A total of 285 HCPs were recruited in this study. The sociodemographic background and professional practice profiles are presented in Table I. The median (IQR) age of the respondents was 37 years (9 years), with most respondents being female (81.8%) and of Malay (84.2%). About half of the respondents attained tertiary education (52.6%). The median (IQR) duration of service in the primary health clinic was 8 years (7 years). In terms of professional roles, about 35.1% were doctors (FMS and medical officers) and 64.9% were non-doctors (pharmacists, medical assistants, and

Table II: The status of the recommendation of HBPM to the hypertensive patients, the usage of HBPM among the patients, and the recognition of HBPM by the HCPs

Variables	n (%)
Recommendation of HBPM by HCPs to their Hypertensive Patients	
Recommendation of HBPM	
Yes	282 (98.9)
No	3 (1.1)
Type of patients that HCPs would recommend HBPM # (n = 282)	
All patients	146 (51.2)
Newly diagnosed patients with hypertension only	150 (52.6)
Already known hypertension only	127 (44.6)
Patients on drug treatment	142 (49.8)
Patients on non-pharmacological treatment	96 (33.7)
Patients with low drug compliance/adherence	110 (38.6)
Barrier when HCPs did not recommend HBPM # (n = 3)	
Lack of guidelines for HBPM	3 (100.0)
Lack of understanding of HBPM	1 (33.3)
Recommendation of HBPM is low in the guidelines	2 (66.6)
No reimbursement for HBPM	1 (33.3)
Scepticism about HBPM	-
Too much burden for physician	2 (66.7)
Concern on reliability and accuracy of HBPM device	3 (100.0)
High cost of the device	3 (100.0)
Inertia of physician on practice of hypertension	-
Usage of HBPM among Hypertensive Patients	
Percentage of hypertensive patients who have BP measurement devices (%)	50.0 (50.0)
Percentage of hypertensive patients who measure their own BP (%)	50.0 (50.0)
Recognition of HBPM as an Effective Intervention by HCPs	
Recognition of HBPM perceived by HCPs	
Highly	184 (64.6)
Moderate to poorly	101 (35.4)
Barrier when HCPs moderate to poorly recognized HBPM # (n = 101)	
Lack of guidelines for HBPM	49 (17.2)
Lack of understanding of HBPM	82 (28.8)
Recommendation of HBPM is low in the guidelines	34 (11.9)
No reimbursement for HBPM	23 (8.1)
Scepticism about HBPM	14 (4.9)
Too much burden for physician	8 (2.8)
Concern on reliability and accuracy of HBPM device	40 (14.0)
High cost of the device	47 (16.5)
Inertia of physician on practice of hypertension	1 (0.4)
HCPs think that recognition of HBPM are perceived by patients	
Highly	139 (48.8)
Moderate to poorly	146 (51.2)
Barrier when HCPs think that their patient moderate to poorly recognized HBPM # (n = 146)	
Lack of understanding of HBPM	120 (42.1)
No Recommendation to patients by physician	45 (15.8)
Scepticism about HBPM	30 (10.5)
Too much burden for patients	55 (19.3)
Concern on reliability and accuracy of HBPM device	70 (24.6)
High cost of the device	94 (33.0)
Low educational level	84 (29.5)
Optimal Practice of HBPM Instruction Methods by HCPs to Their Hypertensive Patients	
Level of optimal instruction practice of HBPM by HCPs to their hypertensive patients	
Optimal practice of HBPM	40 (14.4)
Non-optimal practice of HBPM	245 (85.6)
Awareness of normal home BP level	
Level of awareness of normal home BP reference value	
Good awareness	60 (21.1)
Poor awareness	225 (78.9)

The item is multiple-choice answer where the respondent can choose more than one answer option.

Table III: The assessment of the factors affecting optimal practice of the respondents using simple logistic regression (SLR) and multiple logistic regression (MLR) analysis

Simple Logistic Regression			
Variable	**Crude OR**	**95.0% CI**	**p-value**
Age (Years)	1.02	0.97, 1.07	0.442
Gender			
Male	0.32	0.22, 1.62	0.315
Female	1.00		
Ethnicity			
Others	0.58	0.08, 4.27	0.596
Indian	1.27	0.18, 8.89	0.808
Chinese	0.52	0.10, 2.61	0.427
Malay	1.00		
Educational level			
Primary & secondary education	0.46	0.13, 1.56	0.210
Tertiary education	1.00		
Type of profession			
Doctors	0.34	0.17, 0.67	0.002*
Non-Doctors	1.00		
Duration of practice (Years)	1.02	0.97, 1.08	0.464
Attended HBPM training			
Yes	3.79	1.43, 10.02	0.007*
No	1.00		
Interaction with hypertensive patients (%)	1.01	1.00, 1.02	0.042*
Recommendation of HBPM to hypertensive patients			
Yes	-	-	0.999
No	1.00		
Percentage of hypertensive patients who have HBPM devices (%)	1.01	0.99, 1.02	0.369
Percentage of hypertensive patients who measure their own BP (%)	1.01	1.00, 1.03	0.070
Recognition of HBPM perceived by HCPs			
Highly	1.53	0.73, 3.21	0.260
Moderate to poorly	1.00		
HCPs think that recognition of HBPM are perceived by patients			
Highly	1.92	0.96, 3.81	0.064
Moderate to poorly	1.00		
Level of awareness of normal home BP reference value			
Good awareness	0.33	0.16, 0.67	0.002*
Poor awareness	1.00		
Multiple Logistic Regression			
Variable	**Adjusted OR**	**95.0% CI**	**p-value**
Attended HBPM training			
Yes	3.48	1.29, 9.34	0.013*
No	1.00		

* Significant p-value < 0.05

nurses). The majority of the respondents (76.6%) attended training on HBPM. The median (IQR) percentage of hypertensive patients seen by HCPs in a week was 45.0% (47.5%).

In Table II, almost all HCPs (98.9%) recommended HBPM, with about half (52.6%) doing so for newly diagnosed cases. About 50.0% of patients owned and practised HBPM. Regarding recognition, 64.6% of HCPs perceived HBPM to be highly recognised among themselves, and 48.8% perceived their patients has high recognition on HBPM. However, only 14.4% of HCPs demonstrated optimal practice of HBPM instruction methods. Among those reporting moderate or poor recognition, the most cited barriers were lack of understanding of HBPM (28.8%), lack of guidelines (17.2%), and high device cost (16.5%). HCPs also identified patient-related barriers, including lack of understanding (42.1%), high cost of automatic devices (33.0%), and low education level (29.5%). Only 21.1% of respondents had good awareness of the normal home BP reference value.

Based on Table III, the significant factors associated with optimal practice of instruction methods to hypertensive patients by HCPs from the SLR analysis included attending HBPM training, being a doctor, weekly interaction with hypertensive patients, and good awareness of normal BP level thresholds. In the MLR analysis, attending HBPM training was the only significant associated factor identified. Respondents who attended HBPM training had 3.5 times the odds of practising optimal instruction of HBPM to their hypertensive patients compared to those who did not (adjusted OR 3.48, 95% CI 1.29-9.34, p = 0.013).

DISCUSSION

This study demonstrated that only 14.4% of HCPs practised optimal HBPM instruction methods with their hypertensive patients in the primary health clinics of Putrajaya, indicating that the rest of the patients had not received proper instructions methods on how to perform HBPM effectively. HBPM and other settings outside the clinic, the practice of

HBPM relies entirely on the patient's knowledge and awareness, which in turn depends on the quality of instruction provided by the HCPs. The better the quality of instruction by HCPs, the more effective the HBPM practice among hypertensive patients. This finding shows not much difference with a similar study done among physicians in Japan, where only 10.4 - 12.7% of them provided optimal instruction of HBPM, aligned with the clinical practice guidelines.10 Similarly, a multi-country study revealed that the physicians often recommended HBPM to their patients but failed to ensure correct patient instructions.[17]

In this study, the most frequently reported barrier to HBPM recognition among HCPs (in a sequential manner) was a lack of understanding of HBPM (28.8%), a lack of guidelines (17.2%) and the high cost of BP measurement devices (16.5%). These findings are supported by the Asia HBPM survey study, where nearly half of physicians agreed that lack of understanding of HBPM (49.7%), absence of clear guidelines (49.6%) as important key barriers.[17] From the HCPs' thought and perspective, the top three most significant patient-related barriers were a lack of understanding of HBPM (42.1%), followed by high device cost (33.0%) and low education level (29.5%). Similarly, in the Asia HBPM survey study, 65.5% of physicians cited poor understanding, low education (48.5%), and the high cost of BP measurement devices (44.3%) as major barriers.[17]

This study also demonstrated that attending HBPM training was a significant factor associated with the optimal practice of HBPM instruction methods given by HCPs to their patients (adjusted OR 3.48, 95.0% CI 1.29, 9.34, p = 0.013). This finding is supported by other studies, which demonstrated that structured training significantly improves HCPs' guideline-based BP monitoring instruction and patient counselling quality.[29-31] The evidence clearly demonstrates that HBPM training plays a pivotal role in elevating the standard of patient care. Although other studies often report multiple predictors of HBPM implementation, such as telemonitoring, team-based care, baseline knowledge gaps, HCP self-efficacy, and access to resources.[32-35] Our findings suggest that HBPM training alone is a significant predictor, reflecting unique contextual factors in Malaysia. However, the underlying mechanisms require further exploration, as qualitative research on why training has a disproportionate impact in certain settings remains limited.

The important findings from this study show that the capacity building of the HCPs on HBPM should be enhanced at the primary health clinics. Training of HBPM should be conducted regularly using a variety of modules and involve all levels of professions. To date, there is no available guideline on HBPM in Malaysia. Therefore, we recommend developing national HBPM guidelines as a standard guidance for HCPs. Low education level among hypertensive patients is something that cannot be changed (non-modifiable factor), which also reflects the low literacy and understanding of HBPM practice. However, HCPs who are equipped with the skill set of optimal practice of the HBPM instruction methods may help their patients better understand that practice.

In the situation where the high cost of BP measurement devices is inevitable, the HCPs should have options to offer to their patients, for example, BP measurement can be done at their localities through the "*Komuniti Sihat Perkasa Negara* (KOSPEN)" program, the "*Panel Penasihat Klinik Kesihatan*" Program or the "Pemeriksaan Kendiri" station at the nearest primary health clinics with no cost. Collaboration can be done with the Family Health Development Division, MOH Malaysia, as a stakeholder to incorporate these patient-centred support (HBPM) into existing programs as stated above. These efforts are crucial for enhancing HBPM implementation in Malaysian primary care settings and ensuring that patients benefit from effective HBPM.

STRENGTHS AND LIMITATIONS

To the best of our knowledge, this is among the earliest studies in Malaysia that apply a validated Malay version *i-HBPM* questionnaire and assess the optimal practice of HBPM instruction methods by HCPs to their hypertensive patients at the primary health clinics setting. Most of the studies (including those done in Malaysia) focus on the trend and pattern of HBPM practice among the hypertensive patients, but not the HCPs, who play an essential role in ensuring proper instruction of HBPM practice. Without baseline data in the Malaysian setting, we could not make informed decisions to improve the quality of patient care, particularly in HBPM. A further limitation is that the *i-HBPM* questionnaire, although suitable for measuring HBPM practice patterns, was not originally developed as a predictive instrument. Its use as an outcome in association analysis may therefore introduce construct limitations, and the results should be interpreted cautiously. Future studies should consider validating instruments specifically intended for predictive analysis of HBPM instruction behaviours.

However, this study also has its limitations. First, the majority of the respondents were Malay (84.2%), which does not represent the actual composition of the Malaysian population in terms of ethnicity. Putrajaya is known to be the centre of federal government administration, where most government servants working here are mainly Malays.[36] Participation of the right proportion of other ethnicities in the future study could provide more meaningful findings. Second, Putrajaya is a comparatively urbanised administrative region with better-resourced healthcare facilities and greater capacity for professional development than many rural or semi-urban areas in Malaysia. These contextual features may have facilitated higher levels of HBPM instruction and training uptake among HCPs than might be available in less-urban districts. Accordingly, caution is warranted when extrapolating our results to healthcare providers working in rural settings, remote regions or clinics with more constrained resources. Expanding this study to a larger scale involving different geographical and socioeconomic settings would give us different findings and perspectives.

Furthermore, a small number of respondents with optimal practice (14.4%) may have affected the reliability of the logistic regression model. Low event-per-variable ratios can lead to imprecise parameter estimates, wider confidence

intervals, and instability in regression coefficients. As such, the predictive strength of the model may be constrained, and the results should be interpreted with caution. Thus, larger samples or higher event counts in future studies would strengthen model robustness.

CONCLUSION

This study demonstrated a low prevalence of optimal practice in HBPM instruction methods provided by HCPs to their hypertensive patients at 14.4%, despite a high percentage of HCPs recognising and recommending HBPM to their patients. The findings indicate that HCPs had good attitudes towards the implementation of HBPM to their patients but had limited knowledge on how to instruct their patients in practising HBPM. Regular HBPM training for HCPs is crucial to improve their knowledge and consultation skills on HBPM, subsequently enabling them to assist their patients in practising HBPM.

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CONFLICT OF INTEREST

None.

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Developmental and emotional behavioural outcomes after COVID-19 febrile seizures: A single-centre experience

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ABSTRACT

Introduction: Children with febrile seizures often experience favourable long-term outcomes. However, the outcomes of COVID-19 febrile seizures remain uncertain. The study investigated the developmental and emotional/behavioural outcomes of children with and without COVID-19, presenting with febrile seizures.

Materials and Methods: Participants were families of children with febrile seizures admitted from January to April 2022, during the peak of COVID-19 Omicron variant infection cases. The children were assessed 9-18 months after the seizure event, using the Schedule of Growing Skills II developmental screening tool and their parents completed the Strengths and Difficulties Questionnaire, a measure of emotional/behavioural outcome. A child with positive COVID-19 is characterised by the presence of respiratory symptoms and a positive COVID-19 rapid antigen test. We compared the outcomes of children with and without COVID-19 using Fisher's exact test and Mann-Whitney U test.

Results: Twenty-two families, with 15 (68.2%) COVID-19 and 7 (31.8%) non-COVID-19 febrile seizures participated in the study. A substantial proportion of children from both groups were delayed in various developmental domains (13.6-27.3%), with 9 (40.9%) delayed in 2 or more domains and 2 (9.1%) experienced emotional behavioural difficulties. Children with COVID-19 febrile seizures were not more likely to have developmental delay and emotional/behavioural difficulties.

Conclusions: Children with COVID-19 febrile seizures were not at greater risk of developmental delay or emotional/behavioural difficulties. Further longitudinal studies with a larger sample size are warranted.

KEYWORDS:
Emotion behaviour; child development; COVID-19; febrile seizures

INTRODUCTION

Febrile seizures are the most common seizure in childhood, with an approximately 5% incidence rate that peaks in children 12-18 months of age. Febrile seizures are strongly associated with viral respiratory tract infections, with influenza, adenovirus and parainfluenza viruses among the few common causative viruses. During the COVID-19 pandemic, a surge of febrile seizures associated with SARS-CoV-2 infection was observed, particularly during the Omicron wave in early 2022.[1] The incidence of febrile seizures in children during that period rose significantly from 1.7% during the pre-Omicron era to 14.6%, prompting concerns of potential consequences. Existing evidence has shown that febrile seizures are benign and have favourable outcomes. A population-based study in the UK found no differences observed in the academic, intellectual and behaviour outcomes of 10-year-old children with prior febrile seizures compared to healthy peers.[2] Other studies have similarly shown that children with simple or first febrile seizure did not pose greater developmental and behavioural consequences.[3,4] However, the emergence of COVID-19 infection presenting with febrile seizures raises questions about its benign nature.

COVID-19 has been reported to be associated with adverse neurological outcomes in adults, such as brain fog, memory loss, cognitive deficits, gray matter loss, and brain size shrinkage.5 In children, evidence of chronic neurocognitive symptoms and long-term neurodevelopmental sequelae following COVID-19 infection is less clear.[6] Several studies have shown that children also experience ongoing COVID symptoms and are more frequently to report mental health symptoms.[7,8] Others have opposed, reporting no difference in the frequency of reported post-COVID symptoms among test-positive SARS-CoV-2 infection and control.[9] It is postulated that the impact on children is less apparent, as long-term effects may be mild and not severe enough to warrant a visit to the doctor. The neuropsychological symptoms may also be missed and not captured in parent-reported, or healthcare-provider visit surveys.[10,11] Nevertheless, given the limited studies among children, the potential impact of COVID-19 infection on a child's development cannot be dismissed.[12]

This study similarly sought to enhance the understanding of the long-term developmental consequences of COVID-19 in children. In comparison to previous COVID-19 outcome studies, we focused on children presenting with febrile seizures during an acute infection.8-10 We hypothesised that children with COVID-19 infection presenting with more severe presentation such as febrile seizures have poorer neurodevelopmental outcomes compared to their peers with non-COVID-19 febrile seizures. Therefore, the study aimed to compare the developmental and emotional/behavioural outcomes of children with and without COVID-19 presenting with febrile seizures.

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MATERIALS AND METHODS

Participants

This is a cross-sectional study that recruited children, 18-36 months of age, who were previously hospitalised for febrile seizure at Hospital Tuanku Ja'afar, from January to April 2022. The selection period represents the peak of COVID-19, Omicron incidence among children in Malaysia. We excluded children suspected or diagnosed with neurological or neurodevelopmental disorders, central nervous system infection and children whose COVID-19 infection status was unclear, as further described below. All potential families were contacted via a phone call and parents who agreed were provided an appointment for assessment, 9 to 18 months following the initial hospitalisation. Further information about the study and its procedure was explained in detail to parents on the day of assessment and informed consent was obtained from parents who agreed to enrol. Parents completed a structured questionnaire, while the children's development was assessed by a paediatrician through clinical evaluation. This study was approved by the Joint Committee of Research and Ethics of the IMU University, Malaysia (IMU 563-2022) and Ethics Committee of National Malaysia Research Registry (MRR ID-23-00218-ZXO).

Positive COVID-19 case definition

All hospitalised children with febrile seizures and respiratory symptoms were screened for COVID-19 using antigen detection tests from a nasopharyngeal aspirate as part of the local hospital's policy. A positive rapid antigen detection test result indicates a confirmed COVID-19 case, while a negative result indicates a COVID-19-negative case. We excluded children with febrile seizures who tested negative for COVID-19 but had exposure to a household member with COVID-19 in the preceding 2 weeks before hospitalisation. Additionally, children with evidence of COVID-19 and coinfection, such as positive blood cultures or the presence of other viral pathogens such as respiratory syncytial virus (RSV), influenza A, influenza B, adenovirus, parainfluenza types 1-3 and human metapneumovirus (hMPV) were also excluded.

Measures

The questionnaires distributed to parents include demographic information, existing medical conditions and an emotion/behaviour questionnaire, while additional details of the seizure events were retrieved from medical records. The children's developmental milestones were assessed by a paediatrician who was familiar with the developmental tool and who was not directly involved in their prior treatment. A prior training session was held among the four paediatricians involved, to ensure standardisation of its administration, with adjustments to the local cultural context, particularly in the speech and language domains.

Developmental Outcomes

The Schedule of Growing Skills II (SGS-II) is a developmental screening tool for children aged from birth to five years.[13] It provides a rapid and reliable measure of a child's development through the clinician's assessment of 8 skill domains: posture/ locomotor, manipulative, visual, hearing and language, speech and language, interactive, self-care and cognition. The administration of the guided activities in each subscale would take approximately 20 minutes. The number of successfully completed items will be transferred to the SGS II profile form to obtain the equivalent developmental age for that subscale. The scoring and interpretation of the assessment are based on the developmental quotient (DQ) for each skill area calculated as a ratio of the developmental age (DA) divided by the chronological age (CA) and multiplied by 100.13 DQ (%) = DA / CA x 100) DA is derived from the number of successfully completed items in each skill area and converted using the scoring sheet. DQ cut-off point of DQ < 80 for 0–24-month-old children and DQ < 85 for older than 24 months indicates positive developmental concern. The levels have been shown to be accurate in providing the maximum sensitivity and specificity levels (both more than 0.70.[14] The SGS 2 tool was standardised in the UK, which showed good psychometric properties. The test is validated, reporting an excellent correlation (0.87, $p<0.001$) with Denver Developmental Assessment (DDA), with Cronbach's Alpha reliability analysis of 0.86-0.98, and has been used in a similar study population.[15,16]

Emotion/Behaviour Outcomes

The Strengths and Difficulties Questionnaire (SDQ) is a 25-item parent rating screening measure designed to identify behavioural and emotional problems in children.[17] The instrument comprises of five subscales: conduct problems (e.g., fights with others, well-behaved), hyperactivity (e.g., restless, easily distracted), emotional symptoms (e.g., many worries, often unhappy), peer problems (e.g., picked on or bullied, liked by other children) and prosocial behaviour (e.g., considerate of other people's feelings, shares with other children). Each subscale contains 5 items. Each item is rated on a 3-point response scale from 0= 'not true' to 1= 'somewhat true' and 2= 'certainly true'. Scores from each domain (excluding prosocial behaviour) were summed to generate the 'total difficulties score'. The results score ranges from 0 to 40 with the cut-off scores (17-40) for the 'abnormal' category corresponding to the 90th percentiles. Therefore, total difficulties scores falling in the top 10% of scores based on UK normative population norms are indicative of significant emotional/behavioural difficulties (EBD).[18-19] For each subscale, the scores range from 0 to 10 and scores above the cut-off scores represent clinically significant behaviour. Parents were provided with the questionnaire in both languages; the original English questionnaire and the Malay translated version which are readily available on their official website, Youth in Mind 2022.[19] The parent-rated questionnaires are widely used and have shown acceptable reliability and validity.[209]

Statistical analysis

The data was analysed using Microsoft Excel and SPSS Statistic Package 26. We presented the participant characteristics and outcome measures using medians with interquartile range (IQR) for continuous variables and frequency with percentages for categorical variables. Fisher's exact test and Mann-Whitney U test were utilised to compare outcome measures; developmental quotient and emotion/behaviour scores, between children with COVID-19 febrile seizures and non-COVID-19 febrile seizures. A p-value of <0.05 was deemed statistically significant.

Table I: Characteristics of children with febrile seizures, according to COVID-19 status

	All (N=22)	COVID-19	
		Positive (n=15)	Negative (n=7)
Demographic			
Age at assessment, median (IQR) months	31.0 (5.8)	31.0 (7.0)	31.0 (4.0)
Gender, Female, n (%)	8 (36.4)	10 (66.7)	4 (57.1)
Race, Malay, n (%)	17 (77.3)	12 (80.0)	5 (71.4)
Source of information, n (%)			
Mother	18 (81.8)	13 (86.7)	5 (71.4)
Father	4 (18.2)	2 (13.3)	2 (28.6)
Parent age, median (IQR), years	32.2 (3.78)	31.0 (3.0)	35.0 (9.0)
Parent highest education level			
Primary/ Secondary	12 (54.5)	7 (46.7)	5 (71.4)
College/University	10 (45.5)	8 (53.3)	2 (28.6)
Seizure characteristics, n (%) *			
Age at febrile seizure, median (IQR) months	20.0 (5.8)	21.0 (9.0)	19.0(6.0)
Febrile seizure type			
Simple	17 (77.3)	11 (73.3)	6 (85.7)
Complex	5 (22.7)	4(26.7)	1 (14.3)
Seizure episode			
First **	16 (72.7)	13(86.7)	3 (42.9)
≥ 2	6 (27.3)	2 (13.3)	4 (57.1)
Medical/ Birth History, n (%)			
Family history of febrile seizure	5 (22.7)	2 (13.3)	3 (42.9)
Family history of epilepsy	1 (4.5)	1 (6.7)	0
Subsequent febrile seizure event[†]	17 (77.3)	11 (73.3)	6 (85.7)
Pre-existing health conditions[#]	3 (13.6)	3 (20.0)	0
Pregnancy-related issues[†]	8 (36.4)	5 (33.3)	3 (42.9)

*Febrile seizure during the selection period from January till April 2022.
[†] After the selection period till the time of assessment.
**p<0.05
Asymptomatic congenital heart defect, cow's milk protein allergy, Cleft lip
[†] Gestational diabetes, anaemia

Table II: The comparison of developmental (DQ) and emotional/behavioural outcomes of children with febrile seizures, according to COVID-19 test results

	Total N (%)	COVID-19				p-value*	p-value**
		Positive		Negative			
		Median scores (IQR)	Development concern (DQ<80 or 85) n (%)	Median scores (IQR)	Development concern (DQ<80 or 85) n (%)		
Developmental Quotient (DQ)							
Locomotor	6 (27.3)	95.0 (26.0)	4 (26.7)	100.0 (26.0)	2 (28.6)	0.944	1.000
Manipulative	3 (13.6)	103.0 (15.0)	1 (6.7)	88.0 (33.0)	2 (28.6)	0.417	0.227
Visual	6 (27.3)	129.0 (69.0)	3 (20.0)	83.0 (36.0)	3 (42.9)	0.066	0.334
Hearing and Language	3 (13.6)	107.1 (32.5)	2 (13.3)	93.8 (14.3)	1 (14.3)	0.072	1.000
Speech and Language	4 (18.2)	100.0 (38.0)	3 (20.0)	106.0 (33.0)	1 (14.3)	0.751	1.000
Interaction social	3 (13.6)	97.0 (23.0)	2 (13.3)	100.0 (25.0)	1 (14.3)	0.777	1.000
Self-care	5 (22.7)	126.0 (74.0)	4 (26.7)	137.0 (67.0)	1 (14.3)	0.944	1.000
Cognition	6 (27.3)	103.0 (31.0)	3 (20.0)	86.0 (29.0)	3 (42.9)	0.066	0.334
		Median scores (IQR)	**Behaviour** concerns (> cut-off) n (%)	**Median** scores (IQR)	**Behaviour** concerns (> cut-off) n (%)	**p value***	**p value****
Emotion/Behaviour Scores							
Total Difficulties	2 (9.1)	9.0 (4.0)	1 (6.7)	8.0 (7.0)	1 (14.3)	0.456	1.000
Emotion	2 (9.1)	1.0 (2.0)	2 (13.3)	2.0 (1.0)	0	0.382	1.000
Conduct	3 (13.6)	2.0 (2.0)	1 (6.7)	4.0 (4.0)	2 (28.6)	0.296	0.227
Hyperactivity	0.0	3.0 (2.0)	0	1.0 (5.0)	0	0.173	-
Peer	8 (36.4)	3.0 (2.0)	7 (46.7)	2.0 (1.0)	1 (14.3)	0.126	0.193
Prosocial	1 (4.5)	8.0 (3.0)	1 (6.7)	8.0 (3.0)	0	0.720	1.000

* p- values derived from Mann-Whitney U test to compare medians between groups.
** p-value derived from Fisher's exact test to compare proportions between groups.

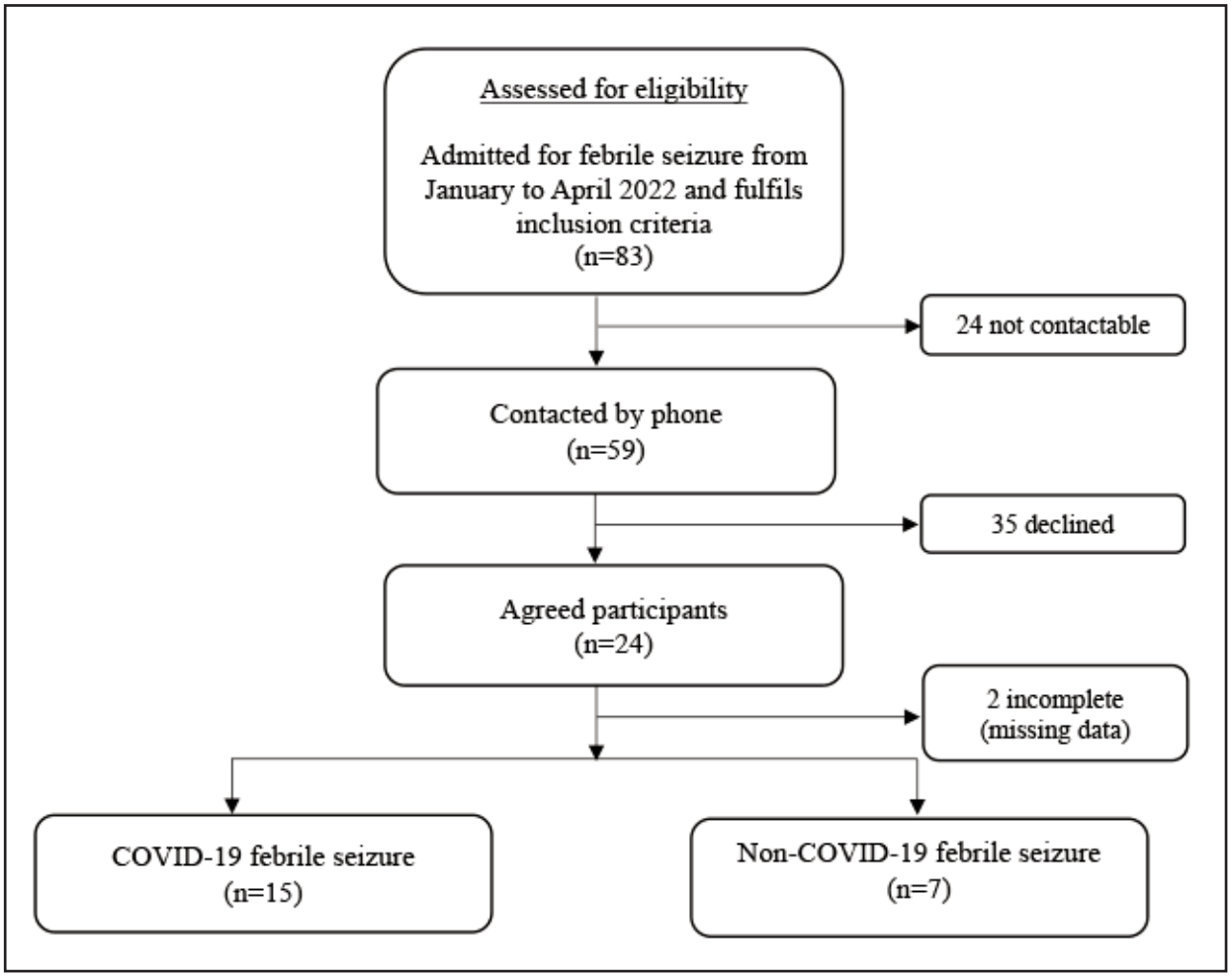

Fig. 1: Flow chart of the participants recruitment to the study

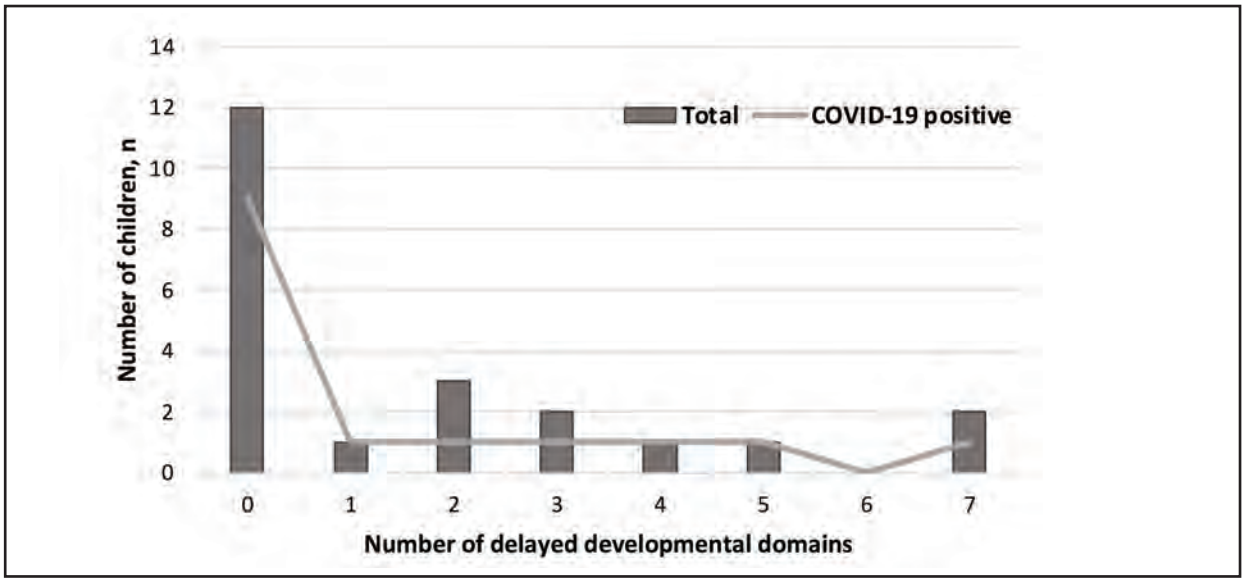

Fig. 2: The number of children according to number of delayed developmental domains

RESULTS

A total of 83 children were admitted for febrile seizure from January to April 2022, of which 24 were not contactable. Among the 59 invited parents, 24 (40.7%) came for their appointments and agreed to participate (Figure I). The final study sample was 22 participants as we excluded two participants with incomplete data. The assessments and data collection were done from November 2022 to July 2023. Compared to study participants, non-participants were of similar age during defined febrile seizure events (median 17.0 (IQR 9) months) and of largely male (65.6%) children.

Table I shows the demographic, seizure characteristics and medical history of the participants. The data was gathered from their accompanying mothers (81.8%) or fathers (18.2%). Among the 22 children, 15 (68.2%) were positive for COVID-19 at the time of the defined febrile seizure. The median age was 31.0 (IQR 5.8) months at the time of assessment and a median age of 20.0 (IQR 5.8) months during their febrile seizure event. The majority were first presentation febrile seizures (16 (72.7%)) and simple seizures (17 (77.3%)). A positive family history of febrile seizure and epilepsy was reported in 5 (22.7%) and 1 (4.5%) child, respectively. None required admission to the intensive care unit (ICU), anti-epileptic prescription, or experienced COVID-19-related complications. Children with COVID-19 febrile seizures were more likely to have first-time febrile seizures (86.7% vs 42.9%, $p < 0.05$). Both groups were otherwise not significantly different in demographic and other medical characteristics.

Figure II illustrates the number of children according to the number of delayed developmental domains. Ten children (45.4%) had developmental delays, with 9 (40.9%) delayed in 2 or more developmental domains. Delays in locomotor, visual and cognition domains were the most common (Table II). The proportion of developmental delays and the median scores for all domains in both groups were not significantly different. (Table II).

The emotion-behaviour scores and proportion of children with emotion-behaviour scores above the cut-off score are displayed in Table II. Two children (9.1%) experienced emotional/behavioural difficulties, with peer problems (8, 36.4%) shown as the predominant symptom. Although peer problems were more commonly reported among children with COVID-19 febrile seizures, the differences in both groups were not statistically significant (46.7% vs 14.3%, p=0.193). The proportion of emotional/behavioural difficulties and the emotion/behaviour median scores of both groups were also not significantly different.

DISCUSSION

Our study observed no differences in the developmental and emotional/behavioural outcomes of children with and without COVID-19 febrile seizures. However, approximately half (45.4%) of the children from both groups were delayed in one or more developmental domains, particularly in the locomotor, visual and cognitive skills. The high numbers in this study exceed pre-pandemic reports of an overall 3.3% developmental delay among children 6-59 months.[21] The results are carefully discussed below, with considerations of the study's limitations.

The association of COVID-19 exposure with early childhood development remains unclear. Studies of infants born to mothers exposed to maternal SARS-CoV-2 infection have reported lower scores in their 8-12 months developmental assessment.[22,23] A study by Jackson et al (2024) of infants exposed to antenatal or neonatal SARS-CoV-2, assessed at 21-32 months of age, showed increased risk of delayed personal-social and social-emotional development as well.[24] However, few studies have shown differing results, demonstrating no risk of developmental delay in all domains during the first 15 months of age.[25,26] As most children with acute COVID-19 infection are usually asymptomatic or experience mild illness, this study focused on outcomes following infection with more severe presentation, specifically febrile seizures. Nevertheless, no association of exposure to COVID-19 infection and developmental delay were demonstrated in this group of children. The effects of COVID-19 infection on brain development in older children may be milder compared to perinatal exposures. Given the limitations of the study, larger sample longitudinal research is still required to substantiate the absence of an association.

Although not the main purpose of the study, our results revealed a high number of developmental delays in this cohort. The findings support the growing evidence of the broader impact of COVID-19 pandemic on early childhood development. A recent study among children below 5 years of age, demonstrated lower scores in their developmental screening assessments in various domains, including communication, problem solving and personal-social compared to pre-pandemic scores.[27] Children born and raised during the pandemic also shown to exhibit lower scores and mental age on the language and communication subscale at 30 months of age compared to pre-pandemic data.[28] The developmental delays are likely attributed to the lack of cognitive stimulation due to restrictions in social activities. Furthermore, parents of children with a history of febrile seizures are likely extra cautious in preventing infection, hence further limiting their children's participation in social events.[29]

The possibility of adverse long-term neurodevelopmental sequelae of febrile seizures should not be disregarded as well.[30] Subtle impairments in cognitive processes, language and behavioural performances, particularly among children with early onset, complex and recurrent febrile seizures have been shown.[4,31,32] Several papers showed delayed vocabulary development, lower developmental scores and lower cognitive function in children with febrile seizures.[4,33] Without a control group in this study, it is difficult to dismiss the potential association between febrile seizure and neurodevelopmental consequences. Lastly, self-selection bias, arising from a higher participation among parents of children with existing developmental concerns, may have also contributed to the elevated detection of developmental delay in this study cohort.

Likewise, emotional/behavioural difficulties was similarly elevated, with our findings showing more than a twofold

increase in peer relationship and conduct problems compared to earlier pre-pandemic study, which reported rates of 9.2% and 5.8%, respectively.[20] A recent local study among preschool children similarly reported higher occurrence of difficulties, reinforcing evidence of the negative impact social isolation has on a child's socioemotional development.[34] Reports of anxiety, fear and depressive symptoms have been described more frequently among children with pre-existing vulnerabilities.[35]

Our study has several limitations that should be considered. First, we encountered a suboptimal participation rate which resulted in a small sample size, limiting both the generalisability of the findings and the statistical power of the study. Second, we employed antigen detection tests to diagnose COVID-19-positive cases. The lack of a more definitive RT-PCR testing may have introduced some diagnostic inaccuracies. However, it is noteworthy that the antigen detection tests had a high positive predictive value during the pandemic's peak, and we meticulously excluded those with negative tests who had close contact with confirmed cases to mitigate this. Third, up to three-quarters of participants experienced recurrent febrile seizures, but the absence of information on their association with COVID-19 infection, presents a confounding factor in assessing the outcomes. The lack of baseline developmental scores and the high selection bias also warrant cautious interpretation of the results.

CONCLUSION

The study did not demonstrate a greater risk of developmental delay or emotional behavioural difficulties among children with COVID-19 febrile seizures. Before dismissing the potential association between COVID-19 and childhood development, a longitudinal population cohort study that addresses the shortcomings of this study is imperative.

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ORIGINAL ARTICLE

Association between irregular eating habits and irritable foods with dyspepsia syndrome in students

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ABSTRACT

Introduction: A group of conditions affecting the upper gastrointestinal tract, known as dyspepsia syndrome, includes epigastric pain, discomfort, bloating, frequent belching, nausea, and vomiting. According to the World Health Organization (WHO) data in 2015, dyspepsia was found to affect 13-40% of the population annually and is listed as one of the top 10 non-communicable diseases in Indonesia that can increase morbidity.

Materials and Methods: This study aimed to investigate the relationship between dietary habits and the prevalence of dyspepsia syndrome among preclinical medical students at the Christian University of Indonesia in the 2023 class. The methodology employed was a descriptive-analytical study, utilizing a cross-sectional approach and a sequential sampling strategy, with 108 participants. This study employed univariate and bivariate analysis as its analytical methods.

Results: The findings of the univariate study revealed that most participants were 18 years old, and 76 women (70.4%) of the total respondents reported experiencing dyspepsia syndrome, accounting for 61.1% of the sample. In this study, bivariate analysis using the Chi-square test revealed a strong correlation (p-value < 0.001) between the incidence of dyspepsia syndrome and diet.

Conclusion: This study concluded that there is a relationship between diet and the development of dyspepsia syndrome.

KEYWORDS:
Dyspepsia syndrome; irregular eating habits; irritable foods; students

INTRODUCTION

Dyspepsia syndrome is a collection of symptoms that indicate a disorder of the upper digestive tract. Symptoms of dyspepsia syndrome consist of pain in the epigastric area (upper middle part of the stomach) or solar plexus, discomfort or a burning sensation spreading in the chest, flatulence, feeling full quickly, frequent belching, nausea, and vomiting. The causes of dyspepsia syndrome are classified into two groups, namely organic dyspepsia and functional dyspepsia. Organic dyspepsia has underlying pathophysiological causes, such as peptic ulcers, cancer, or chronic drug consumption, that cause structural abnormalities in the stomach. In contrast, functional dyspepsia is not based on disease, and no structural abnormalities are found in the stomach.[1]

Based on data from the World Health Organization (WHO) in 2015, it is known that 13-40% of the total population experiences dyspepsia every year.[2] Dyspepsia has a prevalence that varies between 11-29.2% in several countries, such as the United States with a figure of 23- 25.8%, India at 30.4%, New Zealand at 34.2%, Hong Kong at 18.4%, and China at 23.3%[3,4] Based on 2010 Indonesian Health Profile data published by the Indonesian Ministry of Health in 2011, dyspepsia is included in the top 10 diseases of inpatient hospital patients in Indonesia and is in 5th place with the number of patients 24,716 while outpatients are in 6th place with the number of patients 88,599.[2] In Indonesia, especially big cities, have a high incidence of dyspepsia based on information from the Indonesian Ministry of Health 2015 with the incidence of dyspepsia in Surabaya reaching 31.2%, Denpasar 46%, Jakarta 50%, Bandung 32.5%, Palembang 35.5%, Pontianak 31.2%, Medan 9.6%, and Aceh reached 31.7%.[5] According to the Indonesian Health Profile 2020 explains that dyspepsia is still in the top 10 non-communicable diseases that can increase morbidity.[6]

Dyspepsia can be caused by unhealthy eating patterns and lifestyles which include irregular eating schedules, the habit of consuming spicy and sour foods, alcohol, and coffee. These factors can also increase the risk of gastric ulcers due to increased levels of stomach acid.[7] Dyspepsia can also be caused by disorders of gastric motility and anatomy, allergic reactions (hypersensitivity), psychosis, and Helicobacter pylori infection.[8] Research on the relationship between dyspepsia syndrome and pattern eating carried out by Tiana A, et al. (2017) found a correlation of 79.2% between dyspepsia syndrome and irregular eating habits.[9] Nuraini R, et al. (2023) stated that there was a correlation between eating habits and dyspepsia events in preclinical students at the Faculty of Medicine. They found that as many as 89.7% of students with irregular eating habits experienced dyspepsia. Other supporting research was conducted by Suriadi GM, et al. (2024), namely that there is a correlation between irregular eating patterns and the incidence of dyspepsia of 65.7%.[10]

The most significant behaviour that can influence nutritional status is diet. This is because the quantity and quality of food and drinks consumed can influence nutritional intake, which

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in turn can affect the health of individuals and society. If the diet is not changed to include a balanced nutritional intake, this can affect the body's condition and make it more susceptible to non-communicable diseases and other chronic diseases.[11] Three main factors shape the diet: the type, frequency, and amount of food consumed. Irregular eating schedules can interfere with normal stomach function. Gastric emptying can occur due to irregular food consumption, such as skipping meals so that it can reduce the amount of food that enters the stomach. Friction between the stomach walls can cause stomach erosion. Acid reflux is triggered by increased production of stomach acid (HCl) in this condition.[12]

Diet has a significant role in causing dyspepsia syndrome based on studies conducted by Pilichiewicz, et al. (2009) found that 15% of patients experienced dyspepsia due to irregular eating patterns[13] This statement is supported by research by Hassanzadeh S, et al. (2016) explained that having a habit of frequently consuming main foods and additional foods or snacks can influence the incidence of dyspepsia. Skipping meals can cause several problems, including antral hypomotility, delayed gastric emptying, poor gastric accommodation, changes in the gastrin hormone, and acid secretion in the stomach[14] The risk of developing dyspepsia syndrome can increase due to a person's habit of consuming certain foods and drinks that are irritants. such as spicy or sour foods, coffee, alcohol, and carbonated drinks.[2]

Adolescents are included in the group that is vulnerable to dyspepsia syndrome.[2] Adolescence, which is defined as the age range from 12 to 20 years, is a developmental transition from childhood to adulthood, according to Papilia and Olds in Jahja Y (2011).[15] Medical Faculty students have The schedule and activities that must be carried out are very tight, including various activities such as lectures, group discussions, and involvement in non-academic activities, especially for first-year students during the pre-clinical period because they need to adapt to the routine at the Faculty of Medicine. Their busy schedules and activities often interfere with their eating and the types of food they consume daily, resulting in a high risk of dyspepsia in medical students.[2]

Research conducted by Jaber at Gulf Medical University, United Arab Emirates (2016) found that 43.8% of pre-clinical medical students experienced dyspepsia.[16] Another study conducted by Dewi A (2017) showed that among students from the 2015 and 2016 classes of the Hasanuddin University Faculty of Medicine, it was found as many as 97.2% of respondents who consumed food and drinks that could irritate the stomach experienced dyspepsia syndrome.[12] Research conducted by Irfan in 2019 also revealed that 73.3% of pre-clinical students at the Faculty of Medicine at UIN Syarif Hidayatullah Jakarta experienced dyspepsia syndrome which was caused by irregular eating patterns and consumption of food and drinks that could irritate the stomach.[17]

The high incidence of dyspepsia syndrome among medical students makes researchers feel the need to conduct a study that discusses the relationship between diet and the incidence of dyspepsia syndrome in pre-clinical students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia.

MATERIALS AND METHODS

Study design and setting

The methodology used is quantitative research with a cross-sectional study approach and descriptive analysis design. This research aims to understand the correlation between diet and the prevalence of dyspepsia syndrome in pre-clinical studentsclass of 2023 at the Faculty of Medicine, Indonesian Christian University. Data was obtained and analyzed using a research instrument in the form of a questionnaire.

Sample size and sampling technique

Subjects who met the inclusion and exclusion criteria were taken from the population at the Faculty of Medicine, Universitas Kristen Indonesia as research samples. Sequential sampling determines the sample by including all participants who come in a row and meet the research selection criteria until the required number of subjects is met. This is the sampling technique used in this research13.

Research Criteria

Inclusion Criteria: Students from the Faculty of Medicine class of 2023, Universitas Kristen Indonesia who are active and willing to be respondents.

Exclusion Criteria: Students from the Faculty of Medicine, Universitas Kristen Indonesia who are on leave and are not willing to be respondents.

Research Variables

Independent Variable

Free factors are known as independent variables that have an impact on the dependent variable. The independent variable in this study is eating patterns (eating regularly and irritable eating foods and drinks).

Dependent variable

The dependent variable that is influenced or is the result of the independent variable is called the dependent variable. The dependent variable in this study is dyspepsia syndrome.

Data Collection Methods

How to Collect Data

This research uses primary data, namely data obtained directly from research participants through observation and the use of questionnaires.

Data Collection Instruments

This research instrument consisted of 3 questionnaires which were used based on previous research references, namely a dietary pattern questionnaire that asked about eating regularity, irritating foods, and drinks, and a dyspepsia questionnaire based on Rome III criteria. The three questionnaires used in previous research were valid and reliable, then validity and reliability tests were carried out again.

1. Dietary regularity questionnaire
   The questionnaire about eating pattern regularity which consists of meal frequency, meal intervals, and additional foods has 11 questions. Ten questions (numbered 1 to 10) are positive questions and one negative (numbered 11) is a negative question. A Likert scale with options (a), (b), (c), or (d) is used in this questionnaire. Each question with the lowest score is 0 and the maximum score is 3. An overall score of 0 to 16 is irregular eating habits and a score of 17 to 33 is regular eating habits.
2. Irritant food and drink questionnaire
   There are eight negative items on this questionnaire. Likert scale with options (a), (b), (c), or (d). Each question with the lowest score is 0 and the maximum score is 3. An overall score of 0 to 11 assumes that the type of food and drink is not irritating and a score of 12 to 24 is not irritating.
3. Dyspepsia syndrome questionnaire
   The dyspepsia syndrome questionnaire uses 7 questions based on the Rome III Criteria with answer options of "no" or "yes". This questionnaire uses the Guttman scale. Dyspepsia syndrome is positive (+) if the respondent answers "yes" to 1 or more of questions number 1-4 or 2 or more of all questions. Dyspepsia syndrome is negative (-) if the respondent answers "no" to the total question.

Data Analysis Methods

SPSS (Statistical Product and Service Solution) statistical software package and data analysis will be carried out, namely univariate analysis and bivariate analysis.

1. Univariate analysis
   Each variable describes and summarizes the data in table or graph form using univariate analysis. The characteristics of the respondents were known and every variable related to pre-clinical students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia was examined in this research.
2. Bivariate analysis
   The relationship between each independent variable and the dependent variable was examined using the chi-square statistical test with a significance level of p-value <0.05 in SPSS software as part of the bivariate analysis to ensure interaction between the two variables.

RESULTS

Descriptive research on research variables using frequency distribution and percentages and univariate analysis was carried out. The following are details of the univariate analysis of this study, which includes: the subject age and gender; the subject's eating habits, including how often the subject eats and what foods and drinks cause irritation; and the incidence of dyspepsia in 108 students' class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia.

Subject Characteristics Based on Age and Gender

Frequency distribution of respondents based on the age and gender of students at the Faculty of Medicine, Universitas Kristen Indonesia, classified as data in Table I.

Table I above describes the characteristics of respondents based on age among students class of 2023 Faculty of Medicine, Universitas Kristen Indonesia. Of the 108 respondents, there were 2 people aged 17 years (1.9%), 56 people aged 18 years (51.9%), 39 people aged 19 years (36.1%) and 11 people aged 20 years (10.2%). It was found that 18-year-olds had the largest proportion of FK UKI students class of 2023, namely 56 people with a percentage of 51.9%.

This research is in line with research from Putri RN, et al. (2015) regarding the incidence of dyspepsia in students at the Faculty of Medicine, the largest number of respondents at the age of 18 was 94 people (68.1%) based on the age range of 16-19 years.[18] Variations in age frequency in several studies can be caused by differences in age and number of respondents. in several studies. The characteristics of respondents based on gender are 32 people who are male (29.6%) and 76 people who are female (70.4%), so it is known that the female gender dominates this research. It was found that the female gender had the largest proportion among FK UKI students class of 2023, namely 76 people with a percentage of 70.4%.

Research conducted by Tiana A., et al. (2017) explained that the majority of Medical Faculty student respondents who experienced dyspepsia were women with a percentage of 75%.[9] Syah MSF, et al. (2022) have research results in the same direction, namely that the majority of respondents who experienced dyspepsia syndrome were female.[4]

Women are at risk of experiencing dyspepsia compared to men because they try to maintain an ideal body weight and tend to have the wrong body image, such as being afraid of being too thin or fat. Women also have higher levels of the hormones estrogen and progesterone than men. The hormone estrogen has a role in modulating pain responders in the pain recognition pathway when interacting with neurotransmitters. When estrogen hormone levels fluctuate during menstruation, it causes mood swings and impacts visceral pain and gastric motility, so women tend to experience dyspepsia syndrome.[4]

Eating patterns of students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia

a. Eating Regularity

The questionnaire to determine the respondent's eating regularity consisted of 11 questions which were categorized into two, namely regular and irregular. The results of the distribution of respondents are explained in the following table:

Table II explain the results of analysis regarding eating patterns based on eating regularity are obtained. Data has been collected and researched on 108 respondents, 39 people have a regular eating pattern (36.10%), and 69 people have an irregular eating pattern (63.90%). These results state that what dominates is irregular eating patterns among students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia.

Research conducted by Dewi A (2017) is in line with the results of research on students at the Faculty of Medicine, Hasanuddin University, which found that 315 respondents

Table I: Frequency Distribution of Respondents Based on Age and Gender

Characteristic based on	Frequency (n)	Percentage (%)
Age		
17 years	2	1.9
18 years	56	51.9
19 years	39	36.1
20 years	11	10.2
Gender		
Male	32	29.6
Female	76	70.4

Table II: Distribution of Respondents Based on Eating Regularity

Meal Regularity	N	Percentage (%)
Regular	39	36.10%
Irregular	69	63.90%

Table III: Distribution of Respondents Based on Eating Irritable Foods

Irritant foods and drinks	N	Percentage (%)
Not irritating	58	53.7%
Iritative	50	46.3%

Table IV: Frequency Distribution of Respondents Based on the Occurrence of Dyspepsia Syndrome

Dyspepsia Syndrome	N	Percentage (%)
Negative	42	38.9%
Positive	66	61.1%

Table V: Cross Tabulation and Chi-Square Test Between Eating Patterns Based on Eating Regularity and the Incidence of Dyspepsia Syndrome, and Between Irritant Foods and Drinks and the Incidence of Dyspepsia Syndrome

Description	Dyspepsia Syndrome				Total		p-value
	Negative		Positive				
	N	(%)	N	(%)	Number	(%)	
Eating Regularity							
Regular	34	87.2%	5	12.8%	39	100%	<0.001
Irregular	8	11.6%	61	88.4%	69	100%	
Irritant foods and drinks							
Not Irritating	40	69.0%	18	31.0%	58	100%	<0,001
Irritative	2	4.0%	48	96.0%	50	100%	

(51.5%) had irregular eating patterns. Other supporting research results were conducted by Thoriq M, et al. (2023) on students at the Faculty of Medicine, Islamic University of North Sumatra, which showed that 33 respondents experienced irregular eating patterns (55%).[6] Irregular eating patterns could potentially cause dyspepsia syndrome due to students having busy and a lot of activities on campus. A regular eating pattern has a significant impact on gastric acid secretion because this eating pattern can facilitate the stomach's ability to detect food intake patterns and regulate gastric acid production. Irregular eating habits will make it difficult to control stomach acid properly. This condition for a long period cause excessive stomach acid production, thereby increasing the risk of stomach ulcers.[19]

Irritant Foods and Drinks

The questionnaire consisted of 8 questions to find out whether respondents consumed irritating foods and drinks. The results of the distribution of respondents are described in the following table.

Table III explain the results of analysis regarding eating patterns based on foods and drinks irritating were obtained. From the data that was collected and researched on 108 respondents, 58 people did not consume irritating foods and drinks (53.7%), and 50 people consumed irritating foods and drinks (46.3%). The results of this research show that of the 108 students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia. FK UKI 2023, the largest distribution was not to consume food and drinks that could irritate.

The results of research on students at the Hasanuddin University Faculty of Medicine by Dewi A (2017) are in line with this research that the majority of respondents did not consume irritating foods and drinks, amounting to 358 respondents (58.5%).[7] Based on Research conducted by Nuraini R, et al. (2023) among students at the Faculty of Medicine, Wahid Hasyim University, also agreed with the results of this study, namely that 109 respondents did not consume irritating foods and drinks (85%).

The incidence of dyspepsia syndrome in students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia

This questionnaire was conducted to see whether respondents experienced dyspepsia syndrome by categorizing it into two, namely negative and positive. The results of the frequency test of respondents are follows:

The results on Table 5 explain the analysis were obtained based on the incidence of dyspepsia syndrome which consisted of questions regarding dyspepsia syndrome. Data was collected and examined on 108 respondents, 42 people did not show dyspepsia syndrome or were negative (38.9%), and 66 people had dyspepsia syndrome or were positive (61.1%). These results state that those who dominate are positive or experiencing dyspepsia syndrome among students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia.

The results described above are in line with research conducted by Prasetyo AV, et al. (2023) examined students at the Faculty of Medicine, Udayana University, it was found that 202 respondents experienced dyspepsia (75.4%).[17] Another study that explained the distribution of respondents who experienced the highest incidence of dyspepsia was conducted by Irfan (2019) on students at the Faculty of Medicine, UIN Syarif Hidayatullah Jakarta, namely totaling 66 respondents (73.3%).[20] Dyspepsia syndrome can be caused by dietary and environmental factors, psychology, gastric acid secretion, gastrointestinal dysmotility, autonomic dysfunction, and Helicobacter pylori infection.[21] Dietary factors that are at risk of causing dyspepsia include the regularity, frequency, and intervals of eating, breakfast habits, food consumption habits (spicy and sour), and risky drinks (coffee, soda, etc. alcohol).[22] Busy schedules or busy activities on campus can cause students to often neglect their eating habits, thereby increasing the risk of dyspepsia syndrome

Bivariate Analysis

Bivariate analysis was used to determine whether there was a relationship or influence between diet on the incidence of dyspepsia syndrome in students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia. The results of the bivariate analysis of the relationship between diet patterns based on the regularity of eating patterns and irritating foods and drinks with the incidence of dyspepsia syndrome and also between Irritant Foods and Drinks and the incidence of dyspepsia syndrome are described below:

DISCUSSION

Based on the cross-tabulation results in Table V, it is known that of the 39 respondents, there were 34 people had a regular eating pattern, did not experience dyspepsia syndrome (87.2%). There were 5 people had a regular eating pattern and experienced dyspepsia syndrome (12.8 %). There were 69 respondents with irregular eating patterns, 8 respondents did not experience dyspepsia syndrome (11.6%) and 61 other respondents experienced dyspepsia syndrome (88.4%). The results of statistical analysis using the Chi-square correlation test showed that there was a significant relationship between eating patterns based on eating regularity and irritating foods and drinks and the incidence of dyspepsia syndrome in pre-clinical students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia with a p-value <0.001.

This research is in line with that carried out by Thoriq MA, et al. (2023) on students at the Faculty of Medicine, Islamic University of North Sumatra, showed that there was a relationship between the regularity of eating patterns and the incidence of dyspepsia using the Chi-square correlation test with a p-value <0.0016. This research is also in line with research by Prasetyo AV, et al. (2023) on students at the Faculty of Medicine, Udayana University, showed that there was a relationship between eating regularity and the incidence of dyspepsia syndrome, Chi-square correlation test with p-value <0.022.[17]

Meal schedules, meal frequency, and types of food consumed are components that play a role in regular eating patterns. Irregular food consumption, such as skipping meals, will cause a reduction in the amount of food entering the stomach, resulting in gastric emptying, which over a long period will result in erosion of the stomach due to friction between the stomach walls. The increase the production of gastric acid (HCl) which stimulates gastric acid reflux. The impact of irregular eating patterns will cause dyspepsia syndrome such as pain in the epigastric area (upper middle of the stomach) or solar plexus, discomfort or a burning sensation spreading in the chest, flatulence, feeling full quickly, frequent belching, nausea and vomiting.

Based on the cross-tabulation results in Table V, it is known that of the 58 respondents who did not consume irritating foods and drinks, it was found that 40 people did not experience dyspepsia syndrome (69.0%) and 18 people experienced dyspepsia syndrome (31.0%). There were 50 respondents known to consume irritating foods and drinks, which two respondents did not experience dyspepsia syndrome (4.0%) and 48 respondents experienced dyspepsia syndrome (96.0%). The results of statistical analysis using the Chi-square correlation test showed that there was a significant relationship between eating patterns based on irritating foods and drinks and the incidence of dyspepsia syndrome in pre-clinical students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia with a p-value of <0.001.

This research is in line with research conducted by Prasetyo AV, et al. (2023) on students from the Faculty of Medicine, Udayana University, which showed that there was a

relationship between consuming irritating foods and drinks and the incidence of dyspepsia syndrome, Chi-square correlation test with p-value <0.026.[17] Another study conducted by Dewi A (2017) on students from the Faculty of Medicine, Hasanuddin University also stated that that there is a significant relationship between consumption of irritating foods and drinks and the incidence of dyspepsia syndrome in the Chi-square test with a p-value of 0.000.[17]

Dyspepsia syndrome can be caused by consuming irritating foods and drinks, one of which is coffee because it contains caffeine which has the potential to increase stomach acid secretion. Low prostaglandin secretion which protects the stomach and promotes smooth muscle contraction is caused by high gastric acid production. This disrupts gastro-duodenal motility and increases sensitivity thereby causing symptoms of epigastric pain. Increased stomach acid also causes an increase in systemic or local cholecystokinin levels which influence symptoms of early satiety and accelerate the initiation of cholinergic signals from the vagus nerve, causing nausea or vomiting.[23] Foods or drinks that contain gas and are acidic with a low pH of around 3-4 can trigger production. excess gas and accelerates the increase in stomach acid which causes irritation of the stomach and causes symptoms such as flatulence.[2]

Another irritating drink that is at risk of causing dyspepsia syndrome is fizzy drinks. Fizzy drinks contain a lot of gas so when consumed, the gas that is formed is then trapped in the digestive tract which will cause dyspepsia syndromes such as flatulence, frequent belching and nausea.[23] Consuming alcohol can also cause aggressive factors that affect the gastric mucosa, namely reducing defensive factors. Alcohol can also relax the lower esophageal sphincter (LES) resulting in reflux or the return of stomach acid and gas into the esophagus.[24]

Eating fatty foods can worsen dyspepsia due to a condition characterized by delayed gastric emptying and reactivity to gastrointestinal hormones such as cholecystokinin.[25] Spicy foods such as chilies contain the substance capsaicin which changes the way gastrointestinal hormones are secreted and causes the stomach to produce more acid, thereby increasing gastrin synthesis. Lesions and inflammation of the gastric mucosa caused by high levels of stomach acid result in dyspepsia syndrome.[26]

Dyspepsia syndrome can be prevented by administering aloe vera extract because it contains Lemon Juice Concentrate which plays a role in increasing the defense of the gastric mucosa and Chamomile Herb Extract which has anti-inflammatory properties to reduce inflammation in the stomach. Papaya fruit contains proteolytic enzymes that help regenerate damaged stomach cells and reduce or prevent dyspepsia syndrome. The papain enzyme can help in the treatment of dyspepsia syndrome because it contains 11.6% potassium benzylglucosinolate[27] Research conducted by Wang A, et al. (2020) also found that consuming yoghurt made from probiotics containing lactobacillus gasseri showed the effect of reducing dyspepsia symptoms[23] Research by Elliya R, et al. (2022) found that the turmeric plant can be used in traditional medicine because it contains curcumin which can coat the stomach walls due to wounds and functions in reducing stomach acid levels so that it can reduce dyspepsia syndrome.

CONCLUSION

From the processing and analysis of research data, it can be concluded that there is a relationship between eating patterns based on eating regularity and irritating foods and drinks and the incidence of dyspepsia syndrome in pre-clinical students class of 2023 at the Faculty of Medicine, Universitas Kristen Indonesia with a p-value <0.001.

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CONFLICT OF INTEREST

None.

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A retrospective study on patterns of acute chemical poisoning in an urban tertiary hospital in Malaysia

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ABSTRACT

Introduction: Acute poisoning is a frequent reason for emergency department (ED) visits, with varying patterns of presentation across different regions. This study examines the clinical characteristics, sociodemographic factors, and outcomes associated with acute chemical poisoning in a Malaysian population.

Materials and Methods: This is a retrospective case note review of acute chemical poisoning presenting to the ED of a tertiary government hospital in Malaysia from 2016 to 2018. Data were collected on sociodemographic details, clinical presentations, and outcomes, with multiple logistic regression used to identify factors associated with its complications.

Results: A total of 260 cases were included, with 168 (64.6%) being intentional poisonings and 92 (35.4%) accidentals. The majority of patients were single (60.8%), male (58.5%), and of Indian ethnicity (57.3%). The most common agents were pesticides (42.2%). The overall complication rate was 14.2%, and the mortality rate was 4.6%. The most frequent complications were respiratory insufficiency (11.5%) and renal failure (6.5%). Factors significantly associated with complications included intentional poisoning (AOR 3.18, 95% CI 1.05–9.66, p=0.042), ethnicity (Chinese: AOR 12.85, 95% CI 1.40–118.35, p=0.024; other races: AOR 25.99, 95% CI 2.34–238.00, p=0.004), exposure during daytime hours (AOR 12.79, 95% CI 1.52–107.42, p=0.019), and a delay of 2-12 hours before ED visit (AOR 2.30, 95% CI 1.02–5.20, p=0.045).

Conclusion: Acute chemical poisoning is more common in single males with intentional exposures. Important factors associated with its complications include age, ethnicity, the time of exposure, and delayed presentation to the ED.

KEYWORDS:
Poisoning; unintentional poisoning; chemical poisoning; emergency department; toxicology

INTRODUCTION

Poisoning represents a significant public health issue worldwide and is among the leading causes of emergency department (ED) visits. It is defined as exposure to drugs or environmental substances that necessitates medical attention, even if the patient presents with no overt symptoms.[1] Acute poisoning is defined as a single exposure, continuous exposure lasting less than 8 hours, or repeated exposures over a period of up to one week. Poisoning agents are categorized into two main groups: chemicals and pharmaceuticals. Chemical poisonings include household products, pesticides, alcohol, hydrocarbons, and gases, while pharmaceutical poisonings involve over-the-counter medications and prescribed drugs.[2]

In 2016, the World Health Organization estimated that unintentional poisonings resulted in over 100,000 deaths globally; however, the true incidence is likely higher due to underreporting.[3] The wide availability and accessibility of chemicals and their extensive use in medicine, industry, agriculture and daily life contribute to the increased risk of poisoning.

Understanding the epidemiology and determinants of patient outcomes in acute chemical poisoning is crucial for emergency physicians. This knowledge facilitates early diagnosis and prompt treatment, thereby reducing morbidity and mortality.[1] Additionally, it aids in predicting patient outcomes, which can enhance hospital resource utilization and reduce overall burden.

Despite numerous studies on acute poisoning, regional and national data can vary significantly. In Malaysia, research on acute poisoning remains sparse and insufficient.[4] Our study was conducted in the ED of a major public hospital in Malaysia, which handles approximately 175,000 annual ED visits. The objectives of this study were to determine the clinical and sociodemographic patterns of acute accidental and intentional poisonings, and its outcomes within this high-volume ED. The findings aim to assist emergency clinicians in identifying predictive factors for patients' severity, facilitating early recognition of complications, and guiding accurate treatment, ultimately benefiting patient care.

MATERIALS AND METHODS

Study design

This retrospective case note review study was conducted in the Emergency Department of Hospital Tengku Ampuan Rahimah, an urban tertiary public hospital in Selangor, Malaysia. Data were collected from medical records of patients with acute chemical poisoning presenting to the ED

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between January 2016 and December 2018. Cases with pharmaceutical agents or food poisoning, complicated by trauma, and those with incomplete data significant to the study were excluded. Data extraction used a standardized form, capturing sociodemographic details, clinical presentations, chemical agents involved, complications, and outcomes, including admission, hospital length of stay, and mortality.

Statistical analysis

Data were analysed using SPSS version 26.0 (Chicago, IL, USA). Categorical variables are presented as frequencies and percentages, while numerical variables are reported as means and standard deviations. Univariate analysis was conducted using simple logistic regression to identify factors associated with complications. Variables with $p < 0.25$ were included in the multiple logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, with statistical significance set at $p < 0.05$.

Ethical considerations

This study received ethical boards approvals from the Human Research Ethics Committee of USM (USM/JEPeM/18100589) and the Medical Research and Ethics Committee of Ministry of Health Malaysia (NMRR-18-3602-45200 (IIR). The study followed all ethical standards for research without direct contact with human or animal subjects.

Variables definition

Complication refers to an additional disorder or a new feature arising during the course of a disease, injury, or abnormality, which is not an inherent part of the primary condition but may result from it or occur independently.[5,6] In this study, we recorded all complications which included the respiratory system (such as respiratory distress, insufficiency), neurology (altered sensorium and coma, seizure, weakness, numbness), cardiovascular (circulatory shock, arrhythmia, cardiac arrest), gastrointestinal (vomiting, perforation), metabolic and blood disturbances, acute renal failure, and liver failure.[7] Severe complications in this study is defined as complications of Grade 3 (severe or life-threatening symptoms) and 4 (death) based on Poisoning Severity Score (PSS).[8] Intentional poisoning is defined as deliberate self-harm or suicide attempts through ingestion of toxic substances or excessive doses of medication.[2] Unintentional exposure refers to accidental or occupational exposure to harmful substances.

RESULTS

Out of 349 identified patients with acute chemical poisoning, 50 were excluded for meeting the exclusion criteria and 39 for missing data. Thus, 260 cases were included in the study. Among these, 168 (64.6%) had intentional poisoning and 92 (35.4%) were accidental. The mean age of all participants was 44.63 years (SD 16.57). In the accidental poisoning, the mean age was 23.8 years (SD 17.7), with ages ranging from 1 to 75 years. In contrast, the intentional poisoning group had a mean age of 31.76 years (SD 13.12), with ages ranging from 14 to 77 years. The sociodemographic characteristics and clinical presentation of cases are summarized in Table I. The majority of patients were Indian (n=149, 57.3%), followed by Malay (n=49, 18.8%) and Chinese (n=32, 12.3%). Other ethnicities included Kadazan (n=1, 0.4%), Iban (n=1, 0.4%), and several foreign nationals: Nepalese (n=11, 4.2%), Bangladeshi (n=10, 3.8%), Indonesian (n=4, 1.5%), and others (Pakistani, Burmese, and Filipino, n=1 each, 0.4%). Most patients presented to ED early (<2 hours from time of ingestion) (n=143, 55.0%) and having gastrointestinal symptoms (n=217, 79.6%).

This study categorized the chemical agents involved into acids, alkalis, hydrocarbons, gases, insecticides/repellents, herbicides, rodenticides, metals, and miscellaneous agents (e.g., rose water, calamine lotion). A small proportion of patients (n=5, 1.9%) ingested multiple substances. The most common agents were pesticides (n=112, 42.3%), divided into insecticides/repellents (n=52, 19.6%), herbicides (n=46, 17.4%), and rodenticides (n=14, 5.3%). Acids were the second most common group (n=79, 29.8%), with bleach being the most frequent (43 out of 58 intentional cases). Seven cases of accidental mercury poisoning were reported due to a broken thermometer. A summary of chemical agents involved in this study is provided in Table II.

Most of the patients (n=207, 79.6%) developed mild gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhoea. Based on severe complications, the overall complication rate was 14.2%. Severe complications identified in this study are shown in Table III. More patients in the intentional group developed severe complications (n=29/168, 17.2%) compared to accidental poisoning (n=8/92, 8.7%). The highest severe complication was respiratory insufficiency requiring mechanical ventilation (n=30, 11.5%), followed by acute renal failure (n=17, 6.5%). There were 23 (8.8%) patients requiring admission to the Intensive Care Unit (ICU). The mean length of stay for the accidental poisoning was shorter, which was 2.63 days (SD 2.25) from 1 to 21 days compared to the intentional poisoning with 3.65 days (SD 3.75). The overall mortality rate was 4.6% (n=12) and majority died due to exposure to pesticides (paraquat and organophosphate) (n=8, 66.7%).

Simple logistic regression (Table IV) identified age, gender, race, circumstances of poisoning, and latency to ED presentation ($p < 0.25$) as potential factors associated with complications. These variables were included in the multiple logistic regression (Table V). The analysis revealed significant associations between complications and circumstances of poisoning (intentional poisoning AOR 3.18, 95% CI 1.05–9.66, p=0.042), Chinese ethnicity (AOR 12.85, 95% CI 1.40–118.35, p=0.024), and other races (AOR 25.99, 95% CI 2.34–238.00, p=0.004). In terms of clinical presentation, exposure time from 0800 to 1600 hours (AOR 12.79, 95% CI 1.52–107.42, p=0.019), and latency to ED presentation of 2 to 12 hours (AOR 2.30, 95% CI 1.02–5.20, p=0.045) were predictive of complications in acute chemical poisoning.

DISCUSSION

Acute poisoning is a significant global health concern and a leading cause of emergency department visits and hospital admissions.[1,9] Our study found a 14.2% prevalence of complications from acute chemical poisoning, aligning with

Table I: Sociodemographic and clinical presentations of acute chemical poisoning

Variables	Accidental poisoning n=92 n (%)	Intentional poisoning n=168 n (%)	Total N=260 n (%)
Age (years), mean ± SD	23.80 ±17.70	31.67 ±13.12	44.63 ±16.57
Gender			
Male	58 (63.0)	94 (55.9)	152 (58.5)
Female	34 (37.0)	74 (44.1)	108 (41.2)
Race			
Malay	34 (36.9)	15 (8.9)	49 (18.8)
Chinese	12 (13.0)	20 (11.9)	32 (12.3)
Indian	24 (26.0)	125 (74.4)	149 (57.3)
Others	22 (23.9)	8 (4.7)	30 (11.5)
Marital status			
Single	64 (69.6)	94 (55.9)	158 (60.8)
Married	26 (28.3)	69 (41.0)	95 (36.5)
Widowed/divorced	2 (2.1)	5 (2.9)	7 (2.7)
Employment			
Employed	48 (52.2)	70 (41.7)	118 (45.5)
Unemployed	36 (39.1)	58 (34.5)	94 (36.2)
Student	8 (8.7)	40 (23.8)	48 (18.5)
Route of exposure			
Ingestion	63 (68.4)	160 (100)	231 (88.8)
Inhalation	18 (19.6)	0 (0)	18 (6.9)
Others †	11 (11.9)	0 (0)	11 (4.2)
Time of exposure			
0800-1600	44 (47.8)	48 (28.5)	92 (35.4)
1601-2400	42 (45.6)	93 (55.4)	135 (51.9)
0001-0759	6 (6.5)	26 (15.4)	32 (12.3)
Unknown	0 (0)	1 (0.6)	1 (0.4)
Number of agents exposed			
Single	91(98.9)	164 (97.6)	255 (98.1)
Multiple	1 (1.1)	4 (2.4)	5 (1.9)
Underlying medical illness	12 (13.0)	49 (29.2)	61 (23.5)
Underlying psychiatric illness	0 (0)	29 (17.3)	29 (11.2)
Latency time to ED presentation			
< 2 hours	58 (63.0)	85 (50.6)	143 (55.0)
2-12 hours	30 (32.6)	77 (45.8)	107 (41.2)
>12 hours	4 (4.3)	4 (2.4)	8 (3.1)
Unknown	0 (0)	2 (1.2)	2 (0.8)
Systolic blood pressure (mmHg)			
< 90 ‡	6 (6.5)	0 (0)	6 (2.3)
≥ 90	86 (93.5)	168(100.0)	25 (97.7)
Heart rate			
Normal (60-100)	57 (61.9)	109 (64.9)	166 (63.8)
Tachycardia (>100)	34 (36.9)	58 (34.5)	92 (35.4)
Bradycardia (<60)	1 (1.1)	1 (0.6)	2 (0.8)
Temperature (⌖C)			
Normal (36-37.5)	90 (97.8)	159 (94.6)	249 (95.8)
Hyperthermia (>37.5)	2 (2.2)	9 (5.4)	11 (4.2)
Hypothermia (<36)	0 (0)	0 (0)	0 (0)
Gastrointestinal symptoms	52 (56.5)	155 (92.3)	207 (79.6)
Respiratory distress	3 (3.2)	27 (16.1)	30 (11.5)
Altered consciousness	1 (1.1)	13 (7.7)	14 (5.4)

† Skin contact, eye splash

‡ Appropriate for age as they are paediatric population

Table II: Type of agents involved in accidental and intentional acute chemical poisoning

Type of agents	Accidental poisoning N=93 n (%)	Intentional poisoning N=172 n (%)	Total* N=265 n (%)
Acids[a]	21 (22.6)	58 (33.7)	79 (29.8)
Alkali[b]	10 (10.8)	12 (6.9)	22 (8.3)
Hydrocarbons[c]	21 (22.6)	12 (6.9)	33(12.5)
Gases[d]	8 (8.6)	0 (0)	8 (3.1)
Insecticide/Repellant[e]	10 (10.8)	41 (23.8)	52 (19.6)
Herbicide[f]	8 (8.6)	38 (22.1)	46 (17.4)
Rodenticides[g]	6 (6.5)	8 (4.7)	14 (5.3)
Miscellanous[h]	2 (2.2)	2 (1.2)	4 (1.5)
Metal[i]	7 (7.5)	1 (0.6)	8 (3.0)

*Total number of agents is more than number of patients as some patients took multiple agents
a Includes fertilizer, disinfectant (Dettol, flavin, iodine solution), cleaning agent, anti-rustic agent, metal cleaner, toilet bowl cleaner, bleach
b Includes glass cleaner, fertilizer, detergent, hair product, drain opener, battery
c Includes thinner, paint, gasoline, diesel, kerosene, paraffin, acetone, glue, degreaser, toluene, cosmetic, shampoo, soap, moth ball (naphthalene)
d Includes carbon monoxide, cooking gas, smoke
e Includes organophophosphate (malathion, chlorpyrifos, acephate), carbamate, pyrethrim/pyrethroid/neonicotinoids, amitraz, DEET
f Includes paraquat, glyphosate
g Includes non-anticoagulant (zinc phosphide) and anticoagulant (warfarin/super-warfarin)
h Includes rose water prayer, calamine lotion
i Includes mercury

Table III: Outcome of patients with acute chemical poisoning

Variables	Accidental poisoning n=92 n (%)	Intentional poisoning n=168 n (%)	Total N=260 n (%)
Severe complication	8 (8.7)	29 (17.2)	37 (14.2)
Respiratory insufficiency	4 (4.3)	27 (16.1)	30 (11.9)
Cardiac arrhythmia/arrest	2 (2.2)	1 (0.6)	3 (1.2)
Renal failure	4 (4.3)	13 (7.7)	17 (6.5)
Coma	1 (1.1)	13 (7.7)	14 (5.4)
Liver failure	0 (0)	6 (3.6)	6 (2.3)
Circulatory shock	0 (0)	2 (1.2)	2 (0.8)
Intermediate syndrome	0 (0)	6 (3.6)	6 (2.3)
Coagulopathy with bleeding	0 (0)	1 (0.6)	1 (0.4)
Admitted			
General ward	87 (94.5)	148 (88.1)	235 (90.4)
Intensive care unit (ICU)	3 (3.3)	20 (11.9)	23 (8.8)
Not admitted	2 (2.2)	0 (0)	2 (0.8)
Length of stay (days) (mean SD)	2.63 (2.25)	3.65 (3.75)	3.29(3.34)
Final outcome			
Survival	89 (96.7)	159 (94.6)	248 (95.4)
Death	3 (3.3)	9 (5.4)	12 (4.6)

Heyerdahl et al.'s findings of 18%.[7] The fatality rate in our study was 4.6%, predominantly due to pesticide agents (paraquat and organophosphates) which contributed to 66.7% of overall mortality, similar to Eddleston et al.'s report where 60% of deaths were caused by organophosphates.[10] In contrast, Khudair et al.'s study in Qatar reported a lower fatality rate (1.2%), possibly due to better facilities at their teaching hospital, though the specific chemical agents were not detailed.[2]

In terms of sociodemographic, our study found that the majority of patients at our centre were males, which contrasts with other Malaysian studies that report a higher incidence of poisoning among females.[11,12] Additionally, our study identified the Indian ethnicity as having the largest number of poisoning cases, consistent with findings by Fathelrahman et al., where Indians had the highest admission rates for poisoning, even in Penang, where the Chinese population is the majority.[4] This observation aligns with a systematic review on suicide and self-harm in Malaysia, which also indicates a higher prevalence among the Indian ethnic group.[13]

Our study found that the majority of patients intentionally ingested poisonous substances due to various reasons, such as suicidal intent and emotional stress. This aligns with other studies where suicide attempts are the most common cause of poisoning.[14] Ingestion was the most common route of exposure in both accidental and non-accidental cases. In contrast, inhalation was predominantly associated with accidental poisoning, often linked to occupational exposure, particularly among factory workers and cleaners.

Table IV: Simple logistic regression for factors associated with complications in acute chemical poisoning

Variable	Regression coefficient, (b)	Wald (df)	Crude OR (95% CI)	p-value
Age	0.028	6.41 (1)	1.03 (1.01,1.05)	0.011
Gender				
Male	0		1	0.057
Female	-0.75	3.62 (1)	0.47 (0.22,1.02)	
Race				
Malay	0		1	
Chinese	1.88	5.04 (1)	6.58 (1.27,34.08)	0.025
Indian	1.29	2.89 (1)	3.64 (0.82,16.19)	0.089
Others	2.15	6.65 (1)	8.55 (1.67,43.62)	0.010
Marital status				
Single	0		1	
Married	0.34	0.85 (1)	1.40 (0.69,2.85)	0.358
Divorced	0.14	0.16 (1)	1.15 (0.13,10.06)	0.899
Employment				
Employed	0		1	
Unemployed	-0.55	1.89 (1)	0.58 (0.27,1.26)	0.169
Student	-0.93	2.60 (1)	0.40 (0.13,1.22)	0.107
Circumstances				
Accidental	0		1	
Intentional	0.78	3.44 (1)	2.19 (0.96,5.02)	0.063
Route of exposure				
Ingestion	0		1	
Inhalation	-0.32	0.17 (1)	0.72 (0.16,3.29)	0.676
Others*	-0.55	0.26 (1)	0.58 (0.72,4.67)	0.608
Time of exposure				
0800-1600	0		1	
1601-2400	-0.59	2.51 (1)	0.55 (0.27,1.15)	0.113
0001-0759	-1.29	2.78 (1)	0.27 (0.06,1.26)	0.095
No of agent exposed				
Single	0		1	
Multiple	-19.43	0.00 (1)	0.00 (0.00,0.00)	0.99
Latency time to ED presentation				
< 2hours	0		1	
2-12 hours	0.98	6.40 (1)	2.67 (1.25,5.70)	0.011
>12 hours	1.29	2.20 (1)	3.64 (0.66,20.1)	0.138
Underlying medical illness				
Yes	0		1	
No	0.41	1.04 (1)	1.51 (0.69,3.31)	0.309
Underlying psychiatric illness				
Yes	0		1	
No	-0.198	0.12 (1)	0.82 (0.26,2.57)	0.734

Abbreviation: OR Odd Ratio, CI Confidence Interval
*Skin contact, eye splash

Table V: Multiple logistic regression for factors predictive of complications in patients presented with acute chemical poisoning

Variable	Regression coefficient, b	Wald (df)	Adjusted OR (95% CI)	p-value
Circumstances				
Accidental	0		1	
Intentional	1.16	4.153 (1)	3.18 (1.05, 9.66)	0.042
Race				
Malay	0		1	
Chinese	2.55	5.08 (1)	12.85 (1.40, 118.35)	0.024
Others	3.26	8.31 (1)	25.99 (2.84, 238.00)	0.004
Time of exposure				
0001-0759	0		1	
0800-1600	2.55	5.51 (1)	12.79 (1.52, 107.42)	0.019
Latency time to presentation				
<2 hours	0		1	
2-12 hours	0.83	4.01 (1)	2.30 (1.02, 5.20)	0.045

Abbreviation: OR Odd Ratio; CI Confidence Interval
Constant: -7.064
Backward LR elimination method was applied
No multicollinerity and no interaction
Hosmer Lemeshow test, p-value= 0.653
Classification table 87.2% correctly classified
Area under Receiver Operating Characteristic (ROC) curve was 79.0%

In our study, pesticides were the most common chemical agents involved, accounting for 42.3% of cases. This finding is consistent with other studies identifying pesticides as a leading cause of acute poisoning.[4,10] Similarly, a study on drug and chemical poisoning admissions in a Malaysian teaching hospital found that pesticides, particularly insecticides, were the most frequent agents, likely due to their widespread use in households and agriculture, which is a major economic activity in Malaysia.[15] Among the intentional poisonings involving acids, bleach was the most common, reflecting its widespread availability and common use in Malaysian households.

Regarding the presentations of acute poisoning, most patients in our study presented with gastrointestinal symptoms, predominantly vomiting and abdominal pain. These symptoms are common due to gastric irritation caused by the chemical agents while vomiting, a protective mechanism, is the body's attempt to expel harmful substances.[16]

The most common severe complication in our study is respiratory insufficiency. It is a common complication in pesticide poisoning, often resulting from direct toxicity to the alveolar epithelium, as seen in paraquat poisoning.[17] Additionally, cholinergic crisis leading to acute respiratory failure, by central and peripheral mechanisms, are suggested causes following exposure to organophosphates.[18] Renal failure is also a common complication for pesticide group and patients with paraquat poisoning associated with renal injury have high mortality rate.[19,20] One of our patients with accidental organophosphate poisoning developed cardiac arrhythmia which can be due to its direct toxic effect on myocardium.[21]

Our multivariate analysis identified several factors associated with the development of complications: intentional poisoning, Chinese and other races, exposure time (0800-1600), and latency to ED presentation (2-12 hours). Previous studies demonstrate that intentional poisoning is associated with more severe complications and mortality compared to accidental poisoning.[22,23] Those with intentional self-harm often choose more lethal agents or larger doses deliberately designed to cause harm. Common examples include paraquat and organophosphates with high case-fatality rates.[22] In contrast, accidental poisonings usually involve smaller quantities or less toxic household chemicals, leading to milder presentations. Many intentional cases involve chemicals that are far more lethal and concentrated than those in domestic settings, as seen in this study. For example, paraquat ingestion frequently leads to irreversible pulmonary fibrosis and multi-organ failure, even after minimal exposure. Regulatory measures restricting access to such agents have been shown to reduce pesticide-associated mortality and suicide rates.[23]

Although the Indian population comprised the largest group in our study, complications were more common among Chinese patients, consistent with a Singapore study indicating higher medical lethality among Chinese individuals.[24] The higher complication rate among Chinese may be attributed to the lower likelihood of timely intervention, as Indians often attempt suicide in the presence of family, leading to higher rescue rates. Other races, particularly foreign workers in agricultural and chemical industries, are exposed to more harmful industrial-grade or agricultural chemicals. Latency to ED presentation of 2-12 hours was a significant predictor of complications compared to earlier presentation, likely as it limits the effectiveness of early interventions, resulting in more severe systemic toxicity and complications. However, further studies are needed to explore how exposure time affects patient outcomes.

LIMITATIONS

This study has several limitations. It was conducted at a single centre with a small sample size, which may not accurately represent the broader Malaysian population. Additionally, data on the exact amount of chemical substance involved were not available. Information on the treatments received was also lacking, potentially impacting the outcomes. The multiple logistic regression model demonstrated evidence of instability. This finding likely caused by the limited number of outcome events (n = 37 complications). Consequently, the adjusted odds ratios derived from this model should be interpreted with great caution. Larger datasets will be needed to obtain more stable and precise estimates of effect. Future studies should involve a larger sample size, involving multiple centres and nationwide, and include detailed data on the quantity of chemicals involved, and account for the treatment modalities to better understand their effects on patient outcomes.

CONCLUSION

Managing acute chemical poisoning can be challenging to prevent complications. Our retrospective study indicates that acute chemical poisoning is more common among males, Indians, and younger individuals, with pesticides being the most frequent chemical agent involved. The study found a 14.2% complication rate and a 4.6% mortality rate. Predictive factors for complications included intentional poisoning, Chinese and other races, time of exposure, and latency to ED presentation. These findings could inform future management strategies for acute chemical poisoning. However, a larger, well-designed study is needed to more accurately define predictive factors for complications in these patients.

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ORIGINAL ARTICLE

Comparing the administration of rt-PA among stroke fast track patients who arrived by emergency medical services and non-emergency medical services

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ABSTRACT

Introduction: Stroke is a leading cause of death and disability worldwide. Prompt treatment with recombinant tissue plasminogen activator (rt-PA) and endovascular therapy improves outcomes in acute ischemic stroke. Although Emergency Medical Services (EMS) facilitate timely treatment. This study compared rt-PA administration rates and clinical outcomes between patients who arrived via EMS and those who did not in Mueang District, Chachoengsao Province.

Materials and Methods: A retrospective descriptive study was conducted from January 2021 to January 2024, including patients presenting within 4.5 hours of onset, without inter-hospital transfer, and completing 90-day follow-up. Data included transport mode, treatment times, and outcomes.

Results: Of 103 patients, 28 (27.2%) arrived by EMS and 75 (72.8%) by non-EMS. Lipid-lowering agent use was less frequent in the EMS group (17.9% vs. 46.7%, p = 0.008). Onset-to-hospital, door-to-needle, and onset-to-needle times showed no significant differences, and rt-PA administration rates were comparable. In univariable analysis, EMS patients had a higher median NIHSS score than non-EMS patients (median difference = 6.00, 95% CI: 0.99–11.01, p = 0.019), but this was not significant in multivariable analysis (median difference = 0.45, 95% CI: –1.99 - 2.84, p = 0.706). rt-PA was administered in 53.6% of EMS patients and 38.7% of non-EMS patients (p = 0.174). Mechanical thrombectomy was performed more often in EMS patients (42.9% vs. 22.7%, p = 0.043). Discharge NIHSS and 90-day mRS did not differ significantly.

Conclusion: EMS use was associated with greater thrombectomy referral but not with higher rt-PA administration rates or improved outcomes.

KEYWORDS:
Emergency medical services; Ischemic stroke; Patient Outcome Assessment; Stroke Fast Track

INTRODUCTION

Stroke stands as a primary cause of global mortality and long-term disability.[1] Thailand faces particularly high rates of stroke-related death and illness, with acute ischemic stroke incidence on the rise. National data (2009–2021) indicate a significant mortality rate (5.94% to 8.33%) among these patients[2], underscoring stroke's critical public health impact. Beyond patient impact, stroke places a substantial burden on caregivers requiring long-term support. Timely treatment is crucial for improving patient outcomes and family quality of life. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) proves effective within 4.5 hours of symptom onset, with earlier administration significantly boosting survival; each 15-minute delay increases one-year mortality.[3] Endovascular therapy offers another effective intervention, especially for large-vessel occlusions, as per the 2019 AHA guidelines.[4] A Thai study reported high vessel recanalization (92.7%) and favorable outcomes (34.15% at 16 months)[5], supporting its role in stroke care. While Thailand's thrombolytic treatment system has advanced, with rt-PA use increasing from 0.18% to 8.04% (2009–2021)[2], Emergency Medical Services (EMS) utilization remains low (6.6%) 6, despite evidence indicating that EMS transport facilitates faster treatment[7,8]. Consequently, this study aims to compare rt-PA administration rates and treatment outcomes in acute ischemic stroke patients in Mueang District, Chachoengsao Province, between EMS and non-EMS users. The findings will inform strategies to enhance acute stroke care.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Buddhasothorn Hospital (BSH-IRB No. 009/2567). A retrospective descriptive study was conducted, enrolling patients with symptomatic acute ischemic stroke in Mueang District, Chachoengsao Province, between January 1, 2021, and January 31, 2024.

Inclusion criteria were: direct admission to Buddhasothorn Hospital within 4.5 hours of symptom onset, no transfer from another hospital, no symptom onset during hospitalization, and completion of follow-up within 90 days after discharge. Data collected included basic demographics, history of cardiovascular and cerebrovascular diseases, history of drug use, smoking and alcohol consumption, history of antiplatelet or anticoagulant use, vital signs, use of EMS or non-EMS transport, symptoms at hospital admission, time from symptom onset to rt-PA administration, time to laboratory referral, time to brain CT scan, time from hospital arrival to rt-PA administration, referral for mechanical

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Table I: Demographic and clinical characteristics of stroke fast track patients who arrived by emergency medical services and non-emergency medical services. (n = 103)

Characteristics	All patients (n = 103)	EMS (n = 28)	Non-EMS (n = 75)	p-value
Sex				
Female	45 (43.7)	9 (32.1)	36 (48.0)	0.149
Male	58 (56.3)	19 (67.9)	39 (52.0)	
Age (years)	66.15 ± 13.84	65.93 ± 14.27	66.23 ± 13.77	0.923a
Smoking	31 (30.1)	7 (25.0)	24 (32.0)	0.491c
Alcohol drinking	26 (25.2)	5 (17.9)	21 (28.0)	0.292c
Drug abuse	6 (5.8)	2 (7.1)	4 (5.3)	0.662d
Underlying disease				
Hypertension	92 (89.3)	26 (92.9)	66 (88.0)	0.723d
Dyslipidemia	79 (76.7)	20 (71.4)	59 (78.7)	0.439c
Diabetes mellitus	42 (40.8)	9 (32.1)	33 (44.0)	0.276c
Old CVA	10 (9.7)	2 (7.1)	8 (10.7)	0.724d
Ischemic heart disease	11 (10.7)	4 (14.3)	7 (9.3)	0.485d
Atrial fibrillation	13 (12.6)	2 (7.1)	11 (14.7)	0.506d
Old atrial fibrillation	1 (1.0)	0 (0.0)	1 (1.3)	1.000d
Others	18 (17.5)	5 (17.9)	13 (17.3)	1.000d
Medications				
Antihypertensive	63 (61.2)	15 (53.6)	48 (64.0)	0.334c
Lipid-lowering agent	40 (38.8)	5 (17.9)	35 (46.7)	0.008c
Antidiabetic	25 (24.3)	3 (10.7)	22 (29.3)	0.050c
Antiplatelet	14 (13.6)	4 (14.3)	10 (13.3)	1.000d
Anticoagulant	1 (1.0)	0 (0.0)	1 (1.3)	1.000d
Vital sign				
Systolic blood pressure (mmHg)	170.04 ± 30.01	172.36 ± 34.90	169.17 ± 28.18	0.634a
Diastolic blood pressure (mmHg)	94.17 ± 17.32	92.71 ± 20.15	94.72 ± 16.26	0.604a
Pulse rate (bpm)	83.48 ± 14.67	78.89 ± 12.13	85.19 ± 15.24	0.052a
Respiratory rate (rpm)	19.36 ± 1.92	18.79 ± 1.48	19.57 ± 2.04	0.064a
Body temperature (˚C)	36.73 ± 0.43	36.61 ± 0.36	36.78 ± 0.44	0.076a
NIHSS	7 (3 - 16)	12 (3.5 - 17.5)	5 (3 - 16)	0.112b
NIHSS >15 (severe)	28 (27.2)	8 (28.6)	20 (26.7)	0.847c
Glasgow coma scale	15 (11 - 15)	13.5 (11 - 15)	15 (11 - 15)	0.190b
Initial symptoms				
Weakness	64 (62.1)	18 (64.3)	46 (61.3)	0.783c
Dysarthria	6 (5.8)	2 (7.1)	4 (5.3)	0.662d
Ataxia	3 (2.9)	1 (3.6)	2 (2.7)	1.000d
Aphasia	10 (9.7)	2 (7.1)	8 (10.7)	0.724d
Seizure	2 (1.9)	1 (3.6)	1 (1.3)	0.472d
Facial palsy	4 (3.9)	2 (7.1)	2 (2.7)	0.297d
Numbness	10 (9.7)	0 (0.0)	10 (13.3)	0.058d
Coma	4 (3.9)	2 (7.1)	2 (2.7)	0.297d

Data are presented as number (%), mean ± standard deviation or median (interquartile range).
P-value corresponds to aIndependent samples t-test, bMann-Whitney U test, cChi-square test or dFisher's exact test.

Table II: Comparison of duration of treatment between stroke fast track patients who arrived by emergency medical services and non-emergency medical services. (n = 103)

Variables	All patients (n = 103)	EMS (n = 28)	Non-EMS (n = 75)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Onset to ER (min)	106.74 ± 63.54	105.93 ± 67.05	107.04 ± 62.64	0.938
Door to laboratory (min)	30.55 ± 15.14	27.85 ± 9.90	31.54 ± 16.6	0.178
Door to CT (min)	13.29 ± 6.71	12.44 ± 5.32	13.60 ± 7.15	0.446
Door to needle time (min), (n = 46)	36.74 ± 12.07	37.33 ± 12.11	36.45 ± 12.24	0.819
Onset to rt-PA (min), (n = 46)	137.43 ± 52.97	149.47 ± 62.73	131.61 ± 47.59	0.289

†Independent samples t-test

Table III: Comparison of clinical outcomes between stroke fast track patients who arrived by emergency medical services and non-emergency medical services. (n = 103)

Variables	All patients (n = 103)	EMS (n = 28)	Non-EMS (n = 75)	p-value
Receiving rt-PA	44 (42.7)	15 (53.6)	29 (38.7)	0.174[c]
Subgroup NIHSS				
0-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
5-14	23 (63.9)	9 (75.0)	14 (58.3)	0.326[c]
15-24	18 (75.0)	4 (80.0)	14 (73.7)	0.772[c]
≥25	3 (60.0)	2 (66.7)	1 (50.0)	1.000[d]
NIHSS <15	24 (32.0)	9 (45.0)	15 (27.3)	0.146[c]
NIHSS >15	20 (71.4)	6 (75.0)	14 (70.0)	0.791[c]
Refer MT	29 (28.2)	12 (42.9)	17 (22.7)	0.043[c]
MT	14 (13.6)	6 (21.4)	8 (10.7)	0.197[d]
NIHSS at baseline	7 (3 - 16)	12 (3.5 - 17.5)	5 (3 - 16)	0.112[b]
0-4	38 (36.9)	8 (28.6)	30 (40.0)	0.193[d]
5-14	36 (35.0)	12 (42.9)	24 (32.0)	
15-24	24 (23.3)	5 (17.9)	19 (25.3)	
≥25	5 (4.9)	3 (10.7)	2 (2.7)	
NIHSS >15 (severe) at baseline	28 (27.2)	8 (28.6)	20 (26.7)	0.847[c]
NIHSS at discharge	4 (1 - 13)	7 (1 - 18)	3 (1 - 11.5)	0.296[b]
0-4	56 (54.4)	12 (42.9)	44 (58.7)	0.378[d]
5-14	23 (22.3)	8 (28.6)	15 (20.0)	
15-24	9 (8.7)	2 (7.1)	7 (9.3)	
≥25	15 (14.6)	6 (21.4)	9 (12)	
NIHSS >15 (severe) at discharge	24 (23.3)	8 (28.6)	16 (21.3)	0.493[d]
mRS at discharge				
0	26 (25.2)	8 (28.6)	18 (24.0)	0.621[d]
1	21 (20.4)	3 (10.7)	18 (24.0)	
2	9 (8.7)	3 (10.7)	6 (8.0)	
3	4 (3.9)	0 (0.0)	4 (5.3)	
4	5 (4.9)	1 (3.6)	4 (5.3)	
5	26 (25.2)	9 (32.1)	17 (22.7)	
6	12 (11.7)	4 (14.3)	8 (10.7)	
mRS after discharge 90 days				
0	40 (38.8)	12 (42.9)	28 (37.3)	0.798[d]
1	18 (17.5)	3 (10.7)	15 (20.0)	
2	2 (1.9)	0 (0.0)	2 (2.7)	
3	4 (3.9)	1 (3.6)	3 (4.0)	
4	7 (6.8)	3 (10.7)	4 (5.3)	
5	14 (13.6)	3 (10.7)	11 (14.7)	
6	18 (17.5)	6 (21.4)	12 (16.0)	
Change in mRS	27 (26.2)	9 (32.1)	18 (24.0)	0.403[c]

Abbreviations: EMS, emergency medical services; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.
Data are presented as number (%), mean ± standard deviation or median (interquartile range).
p-value corresponds to aIndependent samples t-test, bMann-Whitney U test, cChi-square test or dFisher's exact test.

thrombectomy, receipt of mechanical thrombectomy, NIHSS scores at admission and before discharge, and mRS scores at discharge and at 90 days post-discharge.

Outcome assessment

Outcome measures included the administration of intravenous rt-PA, referral for mechanical thrombectomy, and receipt of mechanical thrombectomy. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 to 42, with higher scores indicating greater severity. Stroke severity was categorized as follows: 0–4 = mild impairment, 5–14 = moderate impairment, 15–24 = severe impairment, and ≥25 = very severe impairment. NIHSS scores were recorded at hospital admission and before discharge. Disability was assessed using the modified Rankin Scale (mRS), which ranges from 0 (no symptoms) to 6 (death), with higher scores indicating greater functional deficits. The mRS was assessed before discharge and at 90 days post-discharge.

Statistical analysis

The baseline demographic and clinical characteristics of acute ischemic stroke patients who arrived by Emergency Medical Services (EMS) and those who arrived without EMS (non-EMS) were presented as frequencies or percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as means ± standard deviation (SD) for normally distributed data or as medians and interquartile ranges for non-normally distributed data, as appropriate. The mean treatment duration between stroke fast-track patients who arrived by EMS and those who arrived by non-EMS was compared using an independent samples t-test. Clinical outcomes between stroke fast-track patients who arrived by EMS and non-EMS were compared using the independent samples t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. To analyze the relationships among dependent and independent variables, including clinical outcomes, between stroke fast-track patients who arrived by EMS and those who arrived by non-EMS, univariate and multivariate

Table IV: Multivariable analyses for comparison of clinical outcomes between stroke fast track patients who arrived by emergency medical services and non-emergency medical services. (n = 103)

Variables	Univariable analysis		Multivariable analysis	
	Absolute difference/ Effect estimate (95% CI)	p-value	Absolute difference/ Effect estimate (95% CI)	p-value
Receiving rt-PA	1.83 (0.76, 4.40)[d]	0.176	1.47 (0.33, 6.48)[d]	0.611
Subgroup NIHSS				
0-4	-	NA	-	NA
5-14	2.14 (0.46, 9.98)[d]	0.331	-	NA
15-24	1.43 (0.13, 16.03)[d]	0.772	-	NA
≥25	2.00 (0.05, 78.25)[d]	0.711	-	NA
NIHSS <15	2.18 (0.75, 6.31)[d]	0.150	5.00 (0.93, 26.86)[d]	0.060
NIHSS >15	1.29 (0.20, 8.29)[d]	0.792	3.44 (0.09, 136.97)[d]	0.511
Refer MT	2.56 (1.02, 6.44)[d]	0.046	4.23 (0.91, 19.70)[d]	0.066
MT	2.28 (0.71, 7.31)[d]	0.164	3.31 (0.45, 24.54)[d]	0.242
NIHSS at baseline	6.00 (0.99, 11.01)[†]	0.019	0.45 (-1.93, 2.84)[†]	0.706
NIHSS >15 (severe) at baseline	1.10 (0.42, 2.89)[d]	0.847	0.32 (0.01, 8.98)[d]	0.502
NIHSS at discharge	4.00 (-0.67, 8.67)[†]	0.092	-1.18 (-4.98, 2.62)[†]	0.538
NIHSS >15 (severe) at discharge	1.48 (0.55, 3.96)[d]	0.441	1.23 (0.18, 8.39)[d]	0.834
mRS at discharge	1.28 (0.58, 2.82)[§]	0.539	0.89 (0.34, 2.34)[§]	0.813
mRS after discharge 90 days	1.02 (0.46, 2.28)[§]	0.953	0.54 (0.19, 1.57)[§]	0.261
Change in mRS	1.50 (0.58, 3.89)[d]	0.405	1.33 (0.43, 4.11)[d]	0.620

Abbreviations: EMS, emergency medical services; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.
[†]Absolute difference is the median difference with 95%CIs from a median regression model.
[d]Effect estimate is odds ratio from a binary logistic regression model.
[§]Effect estimate is odds ratio from a ordinal logistic regression model.

linear regression analyses were performed. A two-sided α level of 0.05 was used for all tests. All analyses were conducted using Stata 17.0 (StataCorp, College Station, TX, USA).

RESULTS

This study aimed to compare the administration of thrombolytic agents (rt-PA) and treatment outcomes between acute ischemic stroke patients who visited Buddhasothorn Hospital with and without the use of the Emergency Medical Services (EMS) system. A total of 103 patients were included in the study, comprising 28 patients (27.2%) in the EMS group and 75 patients (72.8%) in the non-EMS group. The general and clinical characteristics of the patients showed that 56.3% were male, with a mean age of 66.15 ± 13.84 years.

Regarding medication history, the proportions of patients taking antihypertensive drugs were 53.6% in the EMS group and 64.0% in the non-EMS group (p = 0.334). For lipid-lowering agents, the proportions were 17.9% and 46.7%, respectively (p = 0.008). The use of antidiabetic medications was 10.7% in the EMS group and 29.3% in the non-EMS group (p = 0.050).(Table I)

The mean onset-to-hospital arrival time was 105.93 ± 67.05 minutes in the EMS group and 107.04 ± 62.64 minutes in the non-EMS group (p = 0.938). The mean times to laboratory examination and brain CT were 27.85 ± 9.90 and 12.44 ± 5.32 minutes, respectively, in the EMS group, compared with 31.54 ± 16.60 and 13.60 ± 7.15 minutes in the non-EMS group (p = 0.178 and p = 0.446, respectively). Among patients receiving intravenous thrombolysis, the mean door-to-needle time was 37.33 ± 12.11 minutes in the EMS group and 36.45 ± 12.24 minutes in the non-EMS group (p = 0.819), while the mean onset-to-needle time was 149.47 ± 62.73 and 131.61 ± 47.59 minutes, respectively (p = 0.289) (Table II).

A comparative analysis showed that 53.6% of EMS patients and 38.7% of non-EMS patients received thrombolytic therapy (p = 0.174, Table III). EMS users were 1.83 times more likely to receive rt-PA (95% CI: 0.76–4.40, p = 0.176), though not significant after adjustment (Adjusted OR = 1.47, 95% CI: 0.33–6.48, p = 0.611, Table IV). Referral for mechanical thrombectomy (MT) was higher in EMS patients (42.9% vs. 22.7%, p = 0.043, Table III), with a crude OR of 2.56 (95% CI: 1.02–6.44, p = 0.046) and an adjusted OR of 4.23 (95% CI: 0.91–19.70, p = 0.066, Table IV). Among those undergoing MT, 21.4% were EMS users and 10.7% non-EMS (p = 0.197, Table III), with no significant difference after adjustment (Adjusted OR = 3.31, 95% CI: 0.45–24.54, p = 0.242, Table IV). The median NIHSS score at admission was higher in EMS users (12 vs. 5, p = 0.112, Table III), with a significant crude difference (median difference = 6.00, 95% CI: 0.99–11.01, p = 0.019), but nonsignificant after adjustment (adjusted difference = 0.45, 95% CI: -1.93 to 2.84, p = 0.706, Table IV). At discharge, NIHSS was 6.5 for EMS and 3 for non-EMS patients (p = 0.296, Table III), with no significant crude or adjusted differences (Table IV).

At 90 days, functional outcomes by mRS were similar, with most patients achieving mRS 0 (42.9% EMS vs. 37.3% non-EMS, p = 0.798, Table III). Severe disability risk was comparable (Crude OR = 1.02, p = 0.953; Adjusted OR = 0.54, p = 0.261, Table IV). Disability worsening occurred in 32.1% of EMS and 24.0% of non-EMS patients (p = 0.403, Table III), with nonsignificant crude and adjusted odds (Adjusted OR = 1.33, p = 0.620, Table IV).

DISCUSSION

This study found a relatively low utilization rate of Emergency Medical Services (EMS) among acute ischemic stroke patients compared with previous reports [9], though higher than that reported by Gu et al. [10]. The difference may relate to patient selection, as only ischemic strokes within 4.5 hours were included, and to the urban setting of this study, where EMS access is more available.[9,10] Patients with hyperlipidemia were less likely to use EMS, possibly reflecting limited stroke education in NCD clinics.

EMS users presented with higher baseline NIHSS scores, consistent with previous studies[6,8-11] indicating that patients with more severe symptoms are more likely to call EMS. However, onset-to-door, door-to-needle, and onset-to-needle times did not differ significantly between groups. This may be explained by the stroke fast-track system. The lack of significant differences observed in this study highlights the need to refine EMS protocols to incorporate early clinical assessment and the initiation of intravenous antihypertensive therapy in hypertensive patients prior to hospital arrival. Such prehospital interventions could facilitate rt-PA eligibility upon admission and thereby diminish the expected time advantage of EMS utilization.

The rate of rt-PA use did not differ significantly, consistent with Phongphuttha et al. [8] but contrasting with Ekundayo et al. [9] and Gu et al. [10], who reported higher rt-PA administration rates among EMS users. These discrepancies may be due to differences in study design, sample size, or patient selection criteria. Referral for mechanical thrombectomy (MT) was higher among EMS users, reflecting a higher likelihood of large vessel occlusion in this group, though overall MT rates were lower than international reports [12], possibly due to differences in resources or treatment pathways. Functional outcomes at 90 days were similar across groups despite greater initial severity among EMS users, suggesting that rapid in-hospital management mitigated outcome disparities.

Clinically, these findings highlight the role of EMS in identifying severe cases and facilitating MT referral. Enhancing prehospital triage protocols and promoting EMS use among high-risk groups (e.g., diabetes, hyperlipidemia) may improve equity in stroke care. Limitations include the small sample size and single-center, urban setting, which may limit generalizability. Larger multicenter studies are needed to validate these findings and further assess the impact of prehospital interventions on treatment timelines and outcomes.

CONCLUSION

For acute stroke patients admitted to Buddhasothorn Hospital, the receipt of rt-PA treatment did not differ between those who used EMS services and those who did not. Similarly, there were no significant differences in NIHSS scores assessed prior to rt-PA administration and at discharge. Importantly, no significant difference was observed in mRS scores at follow-up, both before and after 90 days.

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ETHICS STATEMENT

This study was approved by the Ethics Committee of Buddhasothorn Hospital (BSH-IRB No. 009/2567). The authors adhered to the applicable EQUATOR Network guidelines (https://www.equator-network.org/) throughout the conduct of this research.

CONFLICT(S) OF INTEREST

None

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Job insecurity and psychological wellbeing among junior doctors in Malaysia: A national cross-sectional study

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ABSTRACT

Introduction: In Malaysia, the rising number of medical graduates has led to a shift from permanent to contract employment in the healthcare system since 2016. This study investigates the impact of employment status on mental health outcomes, job satisfaction, and career perceptions among junior doctors in Malaysia.

Materials and Methods: This nationwide study compared 1,966 contract and 698 permanent junior doctors in Malaysia using validated instruments (Maslach Burnout Inventory, DASS-21, WHOQOL-BREF) and career perception measures.

Results: Contract doctors showed higher depression (adjusted mean 8.72 [95% CI: 8.18-9.26] vs 6.88 [95% CI: 6.25-7.51], p<0.001), anxiety (adjusted mean 6.41 [95% CI: 5.96-6.86] vs. 4.89 [95% CI: 4.36-5.41], p<0.001), stress (adjusted mean 8.74 [95% CI: 8.24-9.23] vs 7.86 [95% CI, 7.28-8.44], p<0.001), emotional exhaustion (adjusted mean 32.14 [95% CI: 30.86-33.42] vs 27.18 [95% CI: 25.68-28.68], p<0.001), and depersonalization (14.10 [95% CI: 13.41-14.80] vs 11.94 [95% CI: 11.13-12.76], p<0.001). Their quality of life was lower in physical (adjusted mean 10.48 [95% CI: 10.30-10.67] vs 11.09 [95% CI: 10.87-11.31], p<0.001), psychological (adjusted mean 11.50 [95% CI: 11.29-11.70] vs 11.86 [95% CI: 11.63-12.10], p<0.001), and environmental domains (adjusted mean 12.42 [95% CI: 12.18-12.65] vs 13.11 [95% CI 12.83-13.38], p<0.001). Contract doctors reported significantly lower satisfaction across multiple domains. Despite similar aspirations to succeed in medicine (OR 0.8 [95% CI: 0.6-1.1], p=0.117), contract doctors reported lower career security (OR 0.04 [95% CI: 0.03-0.05], p<0.001), reduced confidence in specialty training access (OR 0.3 [95% CI: 0.2-0.3], p<0.001), and higher intentions to change careers (OR 5.9 [95% CI: 4.7-7.5], p<0.001) or emigrate (OR 1.9 [95% CI: 1.5-2.3], p<0.001).

Conclusion: Contract employment is associated with poorer mental health, reduced job satisfaction, and diminished career confidence despite similar professional aspirations. These findings suggest current employment practices may threaten healthcare workforce sustainability and highlight the need for policy reforms.

KEYWORDS:
Employment insecurity; Physician burnout; Junior doctors; Psychological distress; Career Satisfaction; Healthcare workforce sustainability

INTRODUCTION

The healthcare profession has traditionally offered high job security, but economic pressures, system reforms, and the COVID-19 pandemic have accelerated a global shift toward contract-based employment.[1-3] This transition has generated considerable job insecurity-defined as the perceived powerlessness to maintain desired continuity in threatened employment circumstances[3]–with significant implications for healthcare delivery and worker wellbeing.[4,5]

Job insecurity affects individuals beyond mere career instability. Evidence suggests that anticipating potential job loss can be as psychologically damaging as actual unemployment, negatively impacting work performance, organizational commitment, and mental health.[6,7] In healthcare context, these effects are particularly concerning as they may directly compromise patient care quality and safety. Meta-analyses consistently demonstrate that job insecurity correlates strongly with poorer job attitudes, diminished satisfaction, and impaired psychological well-being.[4,5,7,8]

In Malaysia, job insecurity has emerged as a critical issue for junior doctors due to structural challenges within the medical workforce pipeline. Following graduation, doctors must complete a mandatory two-year housemanship in public hospitals, followed by service as medical officers before pursuing specialist training. However, a significant surge in medical graduates has overwhelmed the system's capacity to provide permanent positions and training opportunities. To address immediate employment needs, the Malaysian government introduced a contract system in 2016, creating additional challenges related to career progression and job stability.

Junior doctors are particularly vulnerable to these unstable career pathways since the contract system constrains their

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ability to pursue specialist training - a process requiring 8-10 years from graduation to certification. The misalignment between graduate numbers and available training infrastructure undermines both career development and psychological wellbeing. While global research has extensively documented burnout and stress among healthcare workers[9-11], limited attention has been given to how job insecurity specifically affects mental health and well-being among Malaysian junior doctors. This study aims to assess the association between employment status and key outcomes including burnout, emotional distress, and quality of life in this vulnerable professional cohort.

MATERIALS AND METHODS

Study Design and Population

We conducted an anonymous national cross-sectional online survey from July 9 to July 31, 2022. The study targeted junior doctors in Malaysian healthcare system, defined as qualified medical doctors with less than seven years of experience, ranging from housemanship to pre-completion of postgraduate training. Doctors with previously diagnosed psychiatric disorders were excluded from the analysis to focus on work-related factors rather than pre-existing conditions.

Based on Malaysian Medical Association (MMA) registry data, approximately 5,244 junior doctors were practicing in Malaysia during the study period. The study was disseminated via social media, email, and WhatsApp through collaborations with MMA SCHOMOS division and hospital stakeholders. Participants were recruited using convenience and snowball sampling through the Google Forms platform.

We received 2,705 initial responses. After excluding 41 participants with previously diagnosed psychiatric disorders, 2,664 complete responses were included in the final analysis, representing an approximate response rate of 51% from an estimated eligible population of 5,244 junior doctors. All questions in the survey were set as compulsory fields to ensure complete data collection, resulting in no missing data in the final dataset. A participant flow diagram is presented in Figure 1.

Measures

The survey incorporated a validated self-administered tools and custom-designed questions to evaluate physical and mental well-being across employment status categories. The following standardized instruments were employed:

1. **Depression, Anxiety, and Stress Scales 21 (DASS-21):** This instrument assesses psychological distress across three domains using a 4-point Likert scale from "never" (0) to "almost always" (3) and demonstrates robust psychometric properties.[12-14]
2. **Maslach Burnout Inventory (MBI):** This validated measure evaluates burnout across three dimensions: emotional exhaustion (9 items), depersonalization (5 items), and personal accomplishment (8 items). Items are rated on a 7-point Likert scale from "never" (0) to "daily" (6).[15-18]
3. **World Health Organization Quality of Life (WHOQOL-BREF):** This instrument assesses quality of life across four domains: physical health, psychological health, social relationships, and environment.[19,20]

The survey also included demographic questions (gender, age, ethnicity, employment grade, marital status, years of service, and service scheme) and custom items exploring satisfaction, perceptions of organizational efforts, sense of belonging, and responses to employment circumstances.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Descriptive statistics characterized the sample and summarized survey responses. Between-group comparisons (contract versus permanent doctors) employed Chi-square tests for categorical variables and independent samples t-test or Mann-Whitney U tests for continuous variables, as appropriate.

Multiple regression models assessed associations between employment status and outcome measures while adjusting for relevant demographic factors (gender, marital status, and ethnicity). Age, years of service, and job grade were not included as independent covariates due to perfect multicollinearity with employment status- all permanent staff are older medical officers with longer service, while contract staff are predominantly younger house officers/ early-career medical officers.

To address multiple testing across DASS-21, MBI, and WHOQOL-BREF subscales, Bonferroni correction was applied. For perception domains (Table III and IV), multivariable regression analyses were performed with adjustment for gender, marital status, and ethnicity. Effect sizes were calculated using partial eta squared (η^2p) for continuous outcomes and odds ratios for categorical outcomes. Statistical significance was set at $p<0.05$. All results are presented as adjusted means or odd ratios with 95% confidence intervals.

Ethical Consideration

The study adhered to the Declaration of Helsinki principles. Ethical approval was obtained from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR ID-21-1616-60899). All participants provided informed consent prior to survey completion.

RESULTS

Demographic characteristics

Among 2,664 respondents, 1,966 (73.8%) held contract positions and 698 (26.2%) held permanent positions. As shown in Table I, contract doctors were significantly younger (mean age 28.14 vs 31.97 years, $p<0.001$) and more frequently female (62.2% vs 56.3%, $p=0.007$). The ethnic distribution included Malay (42.5%), Chinese (32.3%), and Indian (19.9%) participants, with no significant differences by employment status ($p=0.252$).

Professional status and experience

As detailed in Table I, permanent doctors were exclusively medical officers, while contract doctors included both house officers (43.0%) and medical officers (57.0%). Years of service differed significantly between groups ($p<0.001$), with 15.9%

Table I: Demographic Characteristics of Study Respondents

Variables	Total N= 2664 (%)	Contract n=1966 (%)	Permanent n=698 (%)	p-value*
Gender				
Male	1049 (39.4)	744 (37.8)	305 (43.7)	0.007
Female	1615 (60.6)	1222 (62.2)	393 (56.3)	
Age in years				
mean (SD)	29.14 (2.53)	28.14 (1.71)	31.97 (2.29)	<0.001‡
Ethnicity				
Malay	1133 (42.5)	846 (43.0)	287 (41.1)	
Chinese	861 (32.3)	530 (19.9)	620 (31.5)	
Indian	389 (19.8)	241 (34.5)	141 (20.2)	0.252
Others[a]	140 (5.3)	111 (5.6)	29 (4.2)	
Marital status				
Single	1713 (64.3)	1396 (71.0)	317 (45.4)	
Married	883 (33.1)	524 (26.7)	359 (51.4)	<0.001
Others[b]	68 (2.6)	46 (2.3)	22 (3.2)	
Position				
House officer	846 (31.8)	846 (43.0)	0	
Medical officer	1818 (68.2)	1120 (57.0)	698 (100.0)	<0.001
Year(s) of service				
≤2	1028 (38.6)	1021 (15.9)	7 (1.0)	
3-4	994 (37.3)	642 (24.2)	884 (45.0)	
5-6	61 (3.1)	110 (15.8)	581 (83.2)	<0.001

SD, Standard Deviation
a Other races not specified
b Other marital statuses
* Significant p value are bolded, derived from Pearson Chi-Square unless specified otherwise
‡ Independent t-test

Table II: Depression Anxiety Stress Scales (DASS), Maslach Burnout Inventory (MBI), and World Health Organization Quality of Life (WHOQOL-BREF)

Variables	Total Mean Score (SD)	Contract Mean Score (SD) Adjusted mean (95% CI)	Permanent Mean Score (SD) Adjusted mean (95% CI)	Efect size	p-value*
Depression Anxiety Stress Scales (DASS)					
Anxiety	6.08 (4.82)	6.52 (4.93) 6.41 (5.96, 6.86)[a]	4.84 (4.28) 4.89 (4.36, 5.41)[a]	0.018	<0.001
Depression	8.32 (5.80)	8.85 (5.87) 8.72 (8.18, 9.26)[a]	6.82 (5.36) 6.88 (6.25, 7.51)[a]	0.018	<0.001
Stress	8.51 (5.30)	8.78 (5.36) 8.74 (8.24, 9.23)[a]	7.75 (5.05) 7.86 (7.28, 8.44)[a]	0.005	<0.001
Maslach Burnout Inventory (MBI)					
Emotional exhaustion	30.99 (13.82)	32.38 (13.37) 32.14 (30.86, 33.42)[a]	27.08 (14.30) 27.18 (25.68, 28.68)[a]	0.024	<0.001
Depersonalization	13.21 (7.46)	13.82 (7.44) 14.10 (13.41, 14.80)[a]	11.49 (7.24) 11.94 (11.13, 12.76)[a]	0.015	<0.001
Personal accomplishment	24.37 (9.11)	24.18 (8.86) 25.02 (24.16, 25.88)[a]	24.90 (9.78) 25.57 (24.56, 26.57)[a]	0.001	0.188
WHOQOL-BREF					
Physical Health	10.6 (2.03)	10.44 (2.01) 10.48 (10.30, 10.67)[a]	11.04 (1.99) 11.09 (10.87, 11.31)[a]	0.016	<0.001
Psychological Health	11.49 (2.15)	11.38 (2.15) 11.50 (11.29, 11.70)[a]	11.81 (2.12) 11.86 (11.63, 12.10)[a]	0.005	<0.001
Social Relationships	12.48 (3.29)	12.40 (3.31) 12.99 (12.69, 13.30)[a]	12.70 (3.21) 12.92 (12.57, 13.28)[a]	<0.001	0.631
Environment	12.44 (2.54)	12.28 (2.52) 12.42 (12.18, 12.65)[a]	12.89 (2.55) 13.11 (12.83, 13.38)[a]	0.014	<0.001

SD, Standard Deviation
Note: Each question were analysed independently and the results were derived after controling for sociodemographic data such gender, ethnicity, and marital status in the analysis
a Reported adjusted mean and 95% confidence interval (CI)
*Significant p value are bolded, derived from multiple regression models and adjusted using Bonferroni

Table III: Responses to questions about perceptions relating to job securities

Domains	Total Mean (SD)	Contract Mean (SD) Adjusted mean (95% CI)	Permanent Mean (SD) Adjusted mean (95% CI)	Efect size	p-value*
Job satisfaction as doctor	4.81 (2.47)	4.50 (2.44) 4.60 (4.37, 4.83)[a]	5.71 (2.33) 5.87 (5.61, 6.14)[a]	0.048	<0.001
Doctor welfare preserved	2.80 (2.40)	2.53 (2.29) 2.71 (2.48, 2.93)[a]	3.56 (2.54) 3.80 (3.54, 4.06)[a]	0.038	<0.001
Quality time for self/family	3.18 (2.51)	2.97 (2.38) 3.02 (2.79, 3.25)[a]	3.79 (2.75) 3.79 (3.52, 4.06)[a]	0.018	<0.001
Adequate salary	3.62 (2.65)	3.37 (2.56) 3.43 (3.19, 3.68)[a]	4.33 (2.76) 4.55 (4.26, 4.83)[a]	0.033	<0.001
Exposure to hazards at workplace	7.13 (2.89)	7.08 (3.01) 6.86 (6.59, 7.13)[a]	7.28 (2.52) 7.08 (6.76, 7.40)[a]	0.001	0.095
Career progression opportunities	2.86 (3.06)	1.78 (2.31) 1.66 (1.43, 1.89)[a]	5.93 (2.81) 5.94 (5.67, 6.20)[a]	0.358	<0.001
Do not dare to voice out my welfare issue as I can be disposed anytime	6.99 (3.00)	7.19 (3.01) 7.12 (6.84, 7.40)[a]	6.42 (2.91) 6.30 (5.97, 6.63)[a]	0.014	<0.001
Willing to be deployed as long as given job security	5.24 (3.16)	5.49 (3.19) 5.54 (5.26, 5.84)[a]	4.55 (2.97) 4.76 (4.42, 5.10)[a]	0.012	<0.001
Treatment of contract doctor by other agencies/ministries/ departments	1.53 (1.85)	1.43 (1.81) 1.48 (1.29, 1.67)[a]	1.80 (1.94) 2.19 (1.97, 2.41)[a]	0.022	<0.001
Perception of efforts regarding contract system					
• Ministry of Health Malaysia	0.92 (1.52)	0.79 (1.39) 0.75 (0.61, 0.89)[a]	1.29 (1.78) 1.31 (1.14, 1.47)[a]	0.025	<0.001
• Malaysia Government	0.84 (1.43)	0.74 (1.32) 0.72 (0.59, 0.86)[a]	1.14 (1.67) 1.19 (1.03, 1.34)[a]	0.019	<0.001
• Malaysian Medical Association	4.22 (2.91)	4.22 (2.95) 4.31 (4.04, 4.59)[a]	4.23 (2.79) 4.38 (4.06, 4.70)[a]	<0.001	0.600

SD, Standard Deviation
Note: Each question were analysed independently and the results were derived after controling for sociodemographic data such gender, ethnicity, and marital status in the analysis
a Reported adjusted mean and 95% confidence interval (CI)
* Significant p value are bolded, derived from multiple regression models and adjusted using Bonferroni

of contract doctors having two years or less service, while 83.2% of permanent doctors had served more than five years.

Mental Health and Burnout Outcomes

Table II summarizes the validated assessment outcomes with adjusted means and 95% confidence intervals. After adjusting for gender, marital status, and ethnicity, contract doctors demonstrated significantly higher psychological distress across all DASS-21 dimensions compared to permanent doctors: depression (adjusted mean 8.72 [95% CI: 8.18-9.26] vs 6.88 [95% CI: 6.25-7.51]; p<0.00, η^2p=0.018), anxiety (adjusted mean 6.41 [95% CI: 5.96-6.86] vs 4.89 [95% CI: 4.36-5.41]; p<0.001, η^2p=0.018), and stress (adjusted mean 8.74 [95% CI: 8.24-9.23] vs 7.86 [95% CI: 7.28-8.44]; p=0.001, η^2p=0.005).

On the Maslach Burnout Inventory, contract doctors reported significantly higher scores for emotional exhaustion (adjusted mean 32.14 [95% CI: 30.86-33.42] vs 27.18 [95% CI: 25.68-28.68]; p<0.001, η^2p=0.024). and depersonalization (adjusted mean 14.10 [95% CI: 13.41-14.80] vs 11.94 [95% CI: 11.13-12.76]; p<0.001, η^2p=0.015). No significant difference was observed in personal accomplishment (p=0.188).

Quality of life assessment revealed that contract doctors scored lower in physical health (adjusted mean 10.48 [95% CI: 10.30-10.67] vs 11.09[95% CI: 10.87-11.31]; p<0.001, η^2p=0.016), psychological health (adjusted mean 11.50 [95% CI: 11.29-11.70] vs 11.86 [95% CI: 11.63-12.10]; p=0.001, η^2p=0.005), and environmental domain (adjusted mean 12.24 [95% CI: 12.18-12.65] vs 13.11 [95% CI: 12.83-13.38]; p<0.001, η^2p=0.014). The social relationship domain showed no significant between-group difference (p=0.631).

Job Satisfaction and Security Perceptions

Table III demonstrates significant disparities in job satisfaction and security perceptions between contract and permanent doctors. After adjusting for gender, marital status, and ethnicity, contract doctors consistently reported lower satisfaction scores across multiple domains. They expressed significantly lower satisfaction with their medical career (adjusted mean 4.60 [95% CI: 4.37-4.83] vs 5.87 [95% CI: 5.62-6.14]; p<0.001, η^2p=0.048), perception of doctor welfare preservation (adjusted mean 2.71 [95% CI: 2.48-2.93] vs 3.80 [95% CI: 3.54-4.06]; p<0.001, η^2p=0.038), work-life balance (adjusted mean 3.02 [95% CI: 2.79-3.25] vs 3.79 [95% CI: 3.52-4.06]; p<0.001, η^2p=0.018), salary adequacy (adjusted mean 3.43 [95% CI: 3.19-3.68] vs 4.55 [95% CI: 4.26-4.83]; p<0.001, η^2p=0.033), and career progression opportunities (adjusted mean 1.66 [95% CI: 1.43-1.89] vs 5.94 [95% CI: 5.67-6.20]; p<0.001, η^2p=0.358).

Contract doctors also reported greater dissatisfaction with system-related factors, including treatment by

Table IV: Personal Perception (Self-Reporting Questions)

Variables	Total N= 2664 (%)	Contract n= 1966 (%)	Permanent n= 698 (%)	p-value
1) Career Aspirations				
I wish to succeed as a doctor				
Yes	2343 (88.0)	1717 (87.3)	626 (89.7)	0.101*
No/ Don't know	321 (12.0)	249 (12.7)	72 (10.3)	
OR (95% CI), p value		0.8 (0.6, 1.1)	Reference group	0.117#
I am keen to pursue specialization				
Yes	2285 (85.8)	1703 (86.6)	582 (83.4)	0.035*
No/ Don't know	379 (14.2)	263 (13.4)	116 (16.6)	
OR (95% CI), p value		1.3 (1.0, 1.6)	Reference group	0.067#
I am confident about getting into speciality / subspecialty training				
Yes	518 (19.4)	261 (13.3)	257 (36.8)	<0.001*
No/ Don't know	2146 (80.6)	926 (47.1)	174 (24.9)	
OR (95% CI), p value		0.3 (0.2, 0.3)	Reference group	<0.001#
I have external paper qualifications				
Yes	507 (19.0)	299 (15.2)	208 (29.8)	<0.001*
No	2157 (81.0)	1667 (84.8)	490 (70.2)	
OR (95% CI), p value		0.5 (0.4, 0.6)	Reference group	<0.001#
2) Job Security and Satisfaction				
I feel secure in my career				
Yes	396 (14.9)	61 (3.1)	335 (48.0)	<0.001
No/ Don't know	2268 (85.1)	1720 (87.5)	167 (23.9)	
OR (95% CI), p value		0.04 (0.03, 0.05)	Reference group	<0.001#
I am satisfied with current workload/ working hours				
Yes	585 (22.0)	359 (18.3)	226 (32.4)	<0.001
No/ Don't know	2079 (78.0)	1607 (81.7)	472 (67.6)	
OR (95% CI), p value		0.5 (0.4, 0.6)	Reference group	<0.001#
3) Financial Stabilitiy				
Being a doctor is my primary source of income				
Yes	2570 (96.5)	1900 (96.7)	670 (96.0)	0.421
No/ Don't know	94 (3.5)	66 (3.4)	28 (4.0)	
OR (95% CI), p value		1.2 (0.7, 1.8)	Reference group	0.563#
I have enough saving for future				
Yes	165 (6.2)	79 (4.0)	86 (12.3)	<0.001
No/ Don't know	2499 (93.8)	1887 (96.0)	612 (87.7)	
OR (95% CI), p value		0.3 (0.2, 0.4)	Reference group	<0.001#
I can sustain livelihood if I were to be terminated				
Yes	422 (15.8)	304 (15.5)	118 (16.9)	0.370
No	2242 (84.2)	1662 (84.5)	580 (83.1)	
OR (95% CI), p value		0.9 (0.7, 1.2)	Reference group	0.624#
4) Career Mobility and Alternatives				
Change your career choice				
Yes	1100 (41.3)	988 (50.3)	112 (16.0)	<0.001
No	1564 (58.7)	978 (49.7)	586 (84.0)	
OR (95% CI), p value		5.9 (4.7, 7.5)	eference group	<0.001#
I plan to migrate to other country for better job security/ career progression				
Yes	878 (33.0)	721 (36.7)	157 (22.5)	<0.001
No/ Don't know	1786 (67.0)	1245 (63.3)	541 (77.5)	
OR (95% CI), p value		1.9 (1.5, 2.3)	Reference group	<0.001#

*Significant p-value are bolded, derived from Pearson Chi-Square
#Significant p-value are bolded, derived from logistic regression
OR, Odd Ratio; CI, Confidence Interval

agencies/ministries (adjusted mean 1.48 [95% CI: 1.29-1.67] vs 2.19 [95% CI: 1.97-2.41]; p<0.001, η^2p=0.022), Ministry of Health efforts addressing contract issues (adjusted mean 0.75 [95% CI: 0.61-0.89] vs 1.31 [95% CI: 1.14-1.47]; p<0.001, η^2p=0.025), and government handling of the contract system (adjusted mean 0.72 [95% CI: 0.59-0.86] vs 1.19 [95% CI: 1.03-1.34]; p<0.001, η^2p=0.019). They expressed greater reluctance to voice welfare concerns due to job insecurity (adjusted mean 7.12 [95% CI: 6.84-7.40] vs 6.30 [CI: 5.97-6.63]; p<0.001, η^2p=0.014) and higher willingness to be deployed if given job security (adjusted mean 5.54 [95% CI: 5.26-5.84] vs 4.76 [95% CI: 4.42-5.10], p<0.001, η^2p=0.012). Only two domains showed no significant difference between groups: exposure to workplace hazards (p=0.095) and satisfaction with MMA's efforts addressing contract issues (p=0.600).

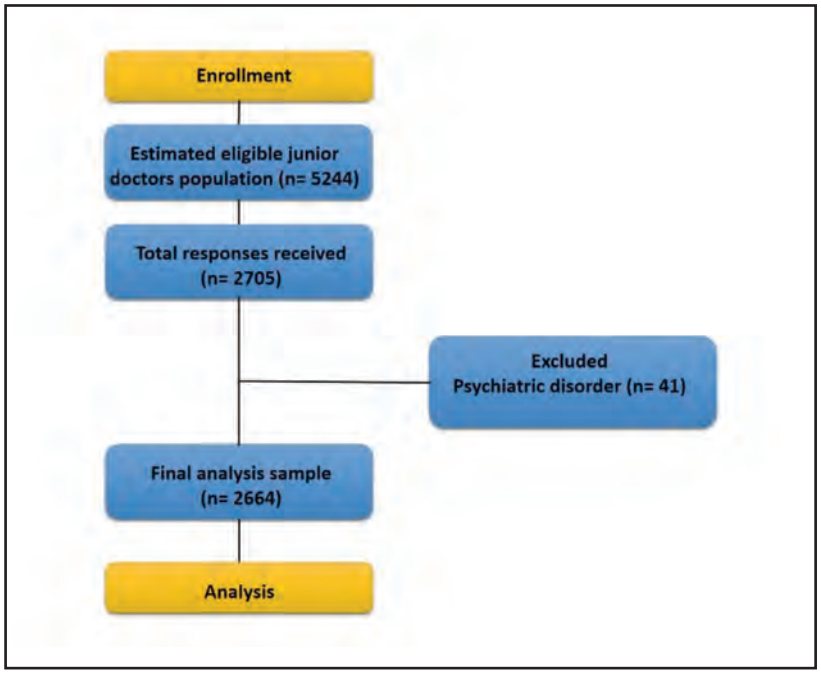

Fig. 1: Demographic Characteristics of Study Respondents

Career Confidence and Future Intentions

Table IV presents findings on personal perceptions organized into four domains that reveal distinct patterns between contract and permanent doctors, with all analyses adjusted for gender, marital status, and ethnicity.

Within the career aspirations domain, both groups similarly aspired to succeed in medicine (87.3% vs. 89.7%, OR 0.8 [95% CI: 0.6-1.1], p=0.117) and pursue specialization (86.6% vs. 83.4%, OR 1.3 [95% CI: 1.0-1.6], p=0.067)). However, contract doctors reported significantly lower confidence in obtaining specialty training (13.3% vs. 36.8%, OR 0.3 [95% CI: 0.2-0.3], p<0.001) and were less likely to possess external qualifications (15.2% vs. 29.8%, OR 0.5 [95% CI: 0.4-0.6], p<0.001).

The job security and satisfaction domain revealed the most striking disparity, with contract doctors significantly less likely to feel secure in their careers (3.1% vs 48.0%, OR 0.04 [95% CI: 0.03-0.05], p<0.001). Contract doctors also reported lower satisfaction with workload and working hours (18.3 vs. 32.4%, OR 0.5 [95% CI: 0.4-0.6], p<0.001).

Despite both groups similarly relying on medical practice as their primary income source (96.7% vs. 96.0%, OR 1.2 [95% CI: 0.7-1.8], p=0.563), the financial stability domain showed that contract doctors were less likely to report having sufficient savings (4.0% vs. 12.3%, OR 0.3 [0.2-0.4], p<0.001). Both groups overwhelmingly reported inability to sustain their livelihood if terminated (84.5% vs. 83.1%, OR 0.9 [95% CI: 0.7-1.2], p=0.624).

These concerns manifested in the career mobility domain, where contract doctors were significantly more likely to consider changing careers (50.3% vs. 16.0%, OR 5.9 [95% CI: 5.9 [4.7-7.5], p<0.001) and contemplating migration for better job security and career progression (36.7% vs. 22.5%, OR 1.9 [95% CI: 1.5-2.3], p<0.001).

Collectively, these findings demonstrate that employment status significantly affects Malaysian junior doctors' career outlook, with contract status associated with greater career uncertainty, financial vulnerability, and consideration of alternative career paths.

DISCUSSION

This national study provides compelling evidence that employment status significantly impacts psychological wellbeing among Malaysian junior doctors. Using validated assessment tools and detailed perception analysis, we identified consistent associations between contract employment and adverse mental health outcomes.

The demographic profile revealed that contract doctors were predominantly younger, earlier in their careers, and more often females compared to their permanent counterparts. This demographic distribution may exacerbate vulnerability to job insecurity effects, as previous research indicates that younger healthcare professionals face elevated risk for job insecurity and its adverse consequences, though associations with gender and socioeconomic status are less consistent.[21,22]

The higher rates of depression, anxiety and stress observed among contract doctors align with broader evidence that perceived job insecurity constitutes a significant risk factor for psychological distress. Meta-analytic findings suggest that job insecurity's impact on mental health may be equal or exceed that of actual unemployment in some contexts.[6,23] Kim & von dem Knesebeck demonstrated that job insecurity

associates with higher risk of depressive symptoms compared to unemployment, with both short and long-term psychological effects.[24] While Theorell et al. found more limited evidence linking job insecurity with depressive symptoms[25], our findings support the growing consensus that insecure work arrangements contribute substantially to psychological distress among healthcare professionals.[26]

The elevated burnout levels among contract doctors, particularly in emotional exhaustion and depersonalization dimensions, are concerning given the global prevalence of burnout among junior doctors (40-50%).[11,27] Our findings parallel those from the United Kingdom, where the 2018 General Medical Council survey identified burnout in nearly 25% of trainees, associated with poor work-life balance, feeling undervalued, inflexible training, and leadership disconnection.[2,28] Our data suggest that employment insecurity may compound these inherent stressors, potentially creating a detrimental cycle where job insecurity increases burnout risk, compromising both patient care quality and professional development.

The stark disparity in career confidence between contract and permanent doctors (3.1% vs 48.0% feeling secure) highlights a critical workforce sustainability challenge. The significantly lower satisfaction with career progression opportunities among contract doctors suggests that employment status affects not only current wellbeing but also long-term career development perspectives. The higher migration intentions among contract doctors (36.7% vs. 22.5%) signals a substantive brain drain risk that could further compromise Malaysia's healthcare capacity and exacerbate workforce shortages.

These findings carry important implications for healthcare workforce planning and policy. The current situation, characterized by widespread job insecurity among junior doctors, threatens both healthcare system sustainability and service quality. Policymakers should implement both immediate interventions to increase permanent positions and long-term structural reforms to address the fundamental mismatch between medical graduate numbers and training infrastructure capacity.

Given the elevated mental health issues among contract doctors, targeted psychological support services should be implemented.[29,30] This might include peer support networks, mentoring programs, regular mental health screening, and early intervention initiatives. To mitigate job insecurity's negative impacts, clear pathways for transitioning from contract to permanent positions, enhanced specialty training opportunities for contract doctors, and structured professional development regardless of employment status are essential. Additionally, addressing factors contributing to burnout–including work-life balance and professional recognition–could partially mitigate job insecurity's negative effects through workload redistribution, improved communication channels, and meaningful recognition programs.

The study's strengths include its large nationwide sample providing robust statistical power, validated assessment instruments, comprehensive domain evaluation, and adjustment for demographic cofounders. To our knowledge, this represents one of the first investigations examining associations between employment status and psychological wellbeing among junior medical doctors during a pivotal career stage when psychosocial stress can significantly influence long-term career trajectories.

Nevertheless, several limitations warrant acknowledgement. First, the use of convenience and snowball sampling introduces potential self-selection bias. Doctors experiencing greater psychological distress may have been more motivated to participate, potentially overestimating the prevalence of adverse outcomes. The inability to determine the exact number of individuals who viewed the survey invitation limits precise response rate calculation, and geographic and professional representativeness could not be ensured. Second, participants with previously diagnosed psychiatric disorders were excluded to focus on work-related factors rather than pre-existing conditions. While this approach was methodologically justified, it may have led to underestimation of the true burden of psychological distress in this population and limits generalizability of findings.

Third, the cross-sectional nature of this study precludes causal inferences regarding the relationship between employment status and psychological outcomes. While we observed significant associations between contractual employment and poor mental health, we cannot determine whether contract status causes these outcomes or whether other unmeasured factors contribute to these differences. Longitudinal studies are needed to elucidate the temporal dynamics of this relationship. Fourth, the use of self-reported measures collected at a single time point introduces potential response bias, social desirability bias, and inability to capture temporal fluctuations in psychological wellbeing and quality of life. Objective measures and repeated assessment would strengthen future investigations.

Fifth, the structural imbalance between contract and permanent groups-where contract doctors are predominantly younger house officers while permanent doctors are exclusively older medical officers- reflects the actual policy implementation in Malaysia. However, we cannot fully disentangle the effects of contractual status from career stage effects. Age, years of service, and job grade could not be included as independent covariates due to perfect multicollinearity with employment status. Sensitivity analyses stratifying by job grade suggest the observed associations persist, but this limitation should be considered when interpreting findings. Finally, for DASS-21 scores, we analyzed continuous scores rather than categorical severity threshold to preserve statistical power and detect subtle differences between groups. While this approach is methodologically sound, future research examining the distribution of severity categories would provide additional clinical context.

Future research should explore potential moderating factors–such as social support networks or individual coping strategies–that may buffer job insecurity's negative effects. Longitudinal studies tracking mental health trajectories

across career transitions would provide valuable insights, as would intervention studies evaluating strategies to mitigate job insecurity's impact on junior doctors' wellbeing.

CONCLUSION

This study provides robust evidence that contract employment status among Malaysian junior doctors associates with poorer mental health outcomes, reduced job satisfaction, and diminished career confidence after adjusting for demographic factors. These findings highlight an urgent need for comprehensive strategies addressing employment security and support mechanisms for contract doctors. The high prevalence of psychological distress and burnout among contract doctors, coupled with elevated migration intentions, suggests that current employment practices may threaten healthcare system sustainability. These findings have implications beyond Malaysia, offering valuable insights for other healthcare systems facing workforce sustainability challenges. Further research and policy development should focus on creating employment models that balance system needs with healthcare workers' well-being and professional development opportunities.

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CONFLICT OF INTEREST

None

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ORIGINAL ARTICLE

Open-window thoracostomy in empyema thoracis: A retrospective review

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ABSTRACT

Introduction: Open-window thoracostomy offers a chance of treatment for cases of empyema thoracis not amenable for closed drainage or decortication. We review herein a collection of 12 cases based on our five years' experience in Kuala Lumpur Hospital, Malaysia performing this procedure.

Materials and Methods: Medical records of open-window thoracostomy cases performed from March 2018 till February 2023 were reviewed retrospectively. Data extracted included demographic information, indication for surgery, surgical approach, perioperative parameters, complications, and 18-months outcome. The primary end point for this study is sepsis resolution. Secondary endpoints are length of stay and spontaneous closure.

Results: 12 patients with mean age of 50.6 years underwent open-window thoracostomy. Five cases of empyema thoracis caused by bronchopleural fistula, five cases of destroyed lung and two recurrent empyema thoracis following unsuccessful decortication. All patients were extubated post-operatively except for two who required postoperative ventilatory support for two days. The primary end point was reached in all cases except one. Three complications were encountered in which blood loss exceeded 750mls.

Conclusions: Open-window thoracostomy may be performed safely in cases of empyema thoracis not amenable for closed drainage or decortication. Preoperative planning, preparation and counselling are vital to ensure good outcome and to manage patient's expectation.

KEYWORDS:
Empyema thoracis, sepsis, open-window thoracostomy

INTRODUCTION

Empyema thoracis, characterised by the accumulation of pus in the pleural cavity, remains a significant public health concern, especially in the context of delayed diagnosis and suboptimal management. It is a progressive pleural disease classically staged into exudative, fibrinopurulent, and organising phases. The transition from conservative therapy to surgical intervention often hinges on clinical judgement, imaging findings, and response to initial management. The morbidity associated with delayed surgical management underscores the need for a stratified and evidence-based approach.

Empyema thoracis typically evolves from a parapneumonic effusion and is classified into three stages:

1. Stage I (Exudative): Free-flowing sterile fluid.
2. Stage II (Fibrinopurulent): Loculated fluid with inflammatory debris.
3. Stage III (Organised): Dense fibrous pleural peel formation.

Failure of nonoperative therapy in stages II–III often necessitates surgery.

Early surgical consultation was advised to pre-empt treatment failure. Louis M, Vivekanandan DD, Grabill N, et al. (2024), in a retrospective-to-prospective transition study, highlighted predictors of tPA/DNase failure, advocating early surgical intervention in high-risk profiles.[1]

Historical data collectively support early surgical referral, especially in cases unresponsive to medical therapy within 48–72 hours. Video-assisted thoracoscopic surgery is increasingly recognised as the preferred surgical modality due to its minimally invasive nature and favourable recovery profile. Furthermore, delayed surgery is associated with increased complications, prolonged hospitalisation, and greater healthcare costs.

In septic patients with persistent space and large bronchopleural fistula, an open-window thoracostomy (OWT) would be required. OWT involves resection of a segment of ribs(s) with suturing of skin flaps to the empyema cavity. This technique is combined with repeated dressing changes to allow complete drainage.

Four separate studies by Ferguson AD, Prescott RJ, Selkon JB, Watson D, Swinburn CR in 1996, Davies CW, Kearney SE, Gleeson FV, Davies RJ. In 1999, Maskell NA, Davies CW, Nunn AJ, et al. in 2005 and Desai G, Amadi W. in 2001 respectively, came to an agreement that rapid recognition of the development of empyema is crucial to successful treatment; even with appropriate therapeutic attempts, the mortality of patients with empyema is 15–20% and higher in immunocompromised patients.[2-5]

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Findings by
a. Eerola S, Virkkula L, Varstela E
b. Shamji FM, Ginsberg RJ, Cooper JD, et al.
c. Van Raemdonck D, Kesteman J, Roekaerts F, Jadoul P
d. Postmus PE, Kerstjens JM, de Boer WJ, Homan van der Heide JN, Koëter GH
e. Shirakusa T, Ueda H, Saito T, Matsuba K, Kouno J, Hirota N.

All strongly assert that these conditions cannot be managed by closed drainage procedures or decortication. Taken together inclusively, they encompass cases of postpneumonectomy empyema, recurrent empyema thoracis post decortication (in which no intact pleural surface is left), mycotic empyema as well as in cases where combination of circumstances renders the patient inoperable.[6-10]

OWT is an option available in the management of such cases. This article is intended to review outcomes of OWT in Kuala Lumpur Hospital, Malaysia between March 2018 till February 2023. The primary endpoint for this study is sepsis resolution, while secondary endpoints are lengths of stay and spontaneous closure.

MATERIALS AND METHODS

Medical records of all patients who underwent OWT at the Thoracic Surgery Unit, Kuala Lumpur Hospital, Malaysia from March 2018 till February 2023 were reviewed retrospectively. All patients who underwent OWT in Kuala Lumpur Hospital, Malaysia within the study period were included in this review. Observational analysis was performed. Informed consent for usage of clinical data was obtained from all patients in this study.

Each and every one of the twelve cases reviewed in this study were determined to have exhausted all other avenues of treatment other than OWT on the basis of following criteria:
- Patient was septic despite on antibiotics and pleural drainage, and too frail to undergo decortication surgery
- Lungs not expanding after decortication with significant space >50% thoracic cavity
- Symptomatic recurrent empyema thoracis following unsuccessful decortication

In all cases, Clagett procedure was used for the OWT, 2 ribs were removed in each case.

Patients' demographic information, indication for surgery, surgical approach, perioperative parameters, and 18 months outcome were reviewed. This study had prior approval of the National Medical Research Register of Malaysia dated 20th of February 2024 (NMRR ID: NMRR ID-23-03712-F80).

Preoperative preparations

Generally, all patients for OWT have undergone contrast-enhanced computed tomography (CT) scan of thorax to assess the severity, bronchopleural fistula, destroyed lungs and the potential space post-surgery. All patients were covered with antibiotics which were targeted according to their respective culture and sensitivity. Those patients who had no culture growth was started on intravenous amoxicillin and clavulanic acid. Of the 12 OWT procedures, one was done under monitored sedation without intubation. Two cases were ventilated via a pre-existing tracheostomy. The rest underwent general anaesthesia with single lung ventilation. Figure 1 depicts the sequential anatomical and procedural steps of OWT.

Treatment of the open cavity

During the first three to four days the dressings were changed under sedation in operation theatre. In the further course, no analgesics or sedative medications were needed. Subsequent treatment was adapted to the individual case.

Closure of the thoracostomy

The wound was allowed to heal by secondary intention considering all the cases have chest wall defects at the thoracostomy site. Information was given about the probability of suboptimal cosmetic result and the possibility of a later myoplastic procedure.

Spontaneous closure following OWT in empyema thoracis

Spontaneous closure of the thoracic window is defined as:
"Complete and sustained obliteration of the thoracostomy wound through native tissue contraction and epithelialisation, occurring without the use of surgical flap reconstruction, thoracoplasty, or secondary closure procedures, and maintaining pleural sterility and structural integrity."

This process must meet the following criteria:
- Wound contraction and epithelialisation: No residual defect communicating with the pleural cavity, confirmed by clinical inspection and, when appropriate, radiological imaging (CT or contrast sinogram).
- Absence of persistent drainage: No evidence of pus or serous fluid output for at least four consecutive weeks.
- Clinical stability: Resolution of systemic signs of infection (e.g., afebrile, normal inflammatory markers).
- Radiological consolidation: CT showing cavity obliteration, lung re-expansion or stabilisation of residual pleural space without loculated effusion.

Spontaneous closure is determined through a combination of clinical, radiological, and microbiological assessments:
1. Clinical Wound Monitoring:
   - Weekly evaluation for reduction in wound diameter, depth, and granulation.
   - Complete epithelial coverage noted by 3 consecutive assessments over a 4-week period.
2. Radiological Confirmation:
   - Chest CT or contrast-enhanced imaging confirms no residual communication with pleural cavity.
   - Used particularly in patients with prior bronchopleural fistula or multiloculated cavities.
3. Microbiological Surveillance:
   - Serial wound cultures to exclude subclinical infection.
   - C-Reactive Protein (CRP) and White Blood Cell Count (WBC) used adjunctively to confirm absence of systemic inflammation.

The time to spontaneous closure post-OWT is highly variable and influenced by patient age, comorbidities, nutritional status, and presence of residual disease. Based on existing cohort studies:

- Median closure time: 4 to 12 months
- Range: 3 months to 2 years

Sepsis resolution in empyema thoracis

Establishing accurate and reproducible criteria for sepsis resolution is essential to inform therapeutic de-escalation, determine discharge readiness, and facilitate longitudinal clinical surveillance. Although significant advances have been made in antimicrobial therapy and surgical management of empyema thoracis, a standardised definition of sepsis resolution remains elusive across diverse clinical settings. Guidelines by Singer M, Deutschman CS, Seymour CW, et al. as well as Mandell LA, Wunderink RG, Anzueto A, et al. are helpful. They are currently, the most widely adopted framework for defining sepsis resolution in empyema thoracis integrating principles from established infectious disease and critical care guidelines, emphasising a tripartite approach encompassing clinical, laboratory, and radiological parameters.[11,12]

1. Clinical Criteria for Sepsis Resolution
   Resolution of sepsis in empyema thoracis from a clinical standpoint entails:

- Afebrile status: Sustained body temperature <38°C for >48 hours without antipyretics.
- Haemodynamic stability: Mean arterial pressure ≥65 mmHg without vasopressor support.
- Improved respiratory parameters: Reduction in dyspnoea, respiratory rate <22/min, and improved oxygen saturation (SpO_2 ≥94% on room air or baseline supplemental O_2).
- Return of gastrointestinal function: Tolerance of enteral feeding.
- Neurological status: Glasgow Coma Scale ≥14 in previously altered mental state patients.

2. Laboratory Biomarkers of Resolution
   Laboratory evidence of resolving systemic inflammation includes:

- WBC: Normalisation or trend toward normal range (4,000–11,000 cells/mm³). A decrease of ≥25% from peak WBC is suggestive of resolution according to Bone RC, Balk RA, Cerra FB, et al.[13]
- CRP: A ≥50% reduction in CRP levels from baseline or peak levels within 72–96 hours post-intervention is indicative of a positive response.
- Procalcitonin (PCT) (optional): When available, PCT <0.5 ng/mL or >80% reduction from peak values reinforces resolution.
- Lactate normalisation: Serum lactate <2 mmol/L.

3. Radiological Indicators of Improvement
   Serial imaging, typically via chest radiograph or CT, should demonstrate:

- Reduction in pleural collection size: Measurable decrease in fluid loculation or cavity volume.
- Re-expansion of adjacent lung: Improved aeration and reduction in atelectasis.
- Resolution of air-fluid levels: Suggestive of cessation of ongoing purulent production.
- Absence of new pleural septations or empyema progression.

Imaging should be obtained post-OWT and ideally within 5–7 days.

a) Empyema Thoracis: Accumulation of purulent material within the pleural cavity causing compression of the underlying lung parenchyma. This stage often correlates with advanced fibrinopurulent or organising-phase empyema.
b) OWT Procedure: A segment of the rib and chest wall is resected to create a sustained opening into the infected pleural cavity, facilitating continuous drainage and aeration. The cavity is packed or irrigated, and secondary closure is delayed.
c) Post-Thoracostomy Cross-Section: A coronal section demonstrates the open communication between the pleural cavity and the external environment through the chest wall defect, enabling effective drainage of infected material.
d) Wound Dressing and Maintenance: Postoperative care includes sterile dressing changes and wound inspection to prevent superinfection and promote granulation tissue formation as part of delayed wound healing strategies.

This figure supports the clinical decision-making process and anatomical considerations inherent to the OWT technique, often employed in cases of chronic or refractory empyema thoracis.

Statistical Analysis

Quantitative variables namely; age, BMI, duration of surgery and blood loss were expressed in mean, median and interquartile ranges. Qualitative variables on the other hand specifically gender and comorbidity were expressed as frequency (%).

Preliminary analysis and retrospective observational study were specific to each category starting from demographic to outcomes. (Refer Tables I -III)

RESULTS

From March 2018 till February 2023, 12 patients with mean age of 50.6 years (range: 36 - 65 years) presented with empyema thoracis of which 11 were males and one female. Out of the 12 cases, 11 were active smokers. Mean body mass index was 22.3, ranging from 17 to 35.2. (refer Table II a.) With respect to comorbidities (table II b.), eight cases had underlying active pulmonary tuberculosis, six were diabetics, two were hypertensive and two were hepatitis C carriers. Preoperative ventilation status ranges from room air to face mask. None of the cases had invasive respiratory support preoperatively.

The most consistent presenting symptom seen was dyspnoea (nine cases). Chronic cough was seen in seven cases. Seven cases experienced significant unintentional weight loss. Fever was seen in four cases together with anorexia. Two had reduced effort tolerance and pleuritic chest pain. Pleurocutaneous fistula was seen in two cases in which there was purulent discharge from previous thoracotomy scar or chest tube site. Other symptoms encountered includes night

Table I: Multiple study comparative analysis of empyema thorcis indication, complication rate, recovery time and length of hospital stay

SURGICAL METHOD	INDICATION STAGE	HOSPITAL STAY	COMPLICATION RATE	RECOVERY TIME
VATS*	Stage II-III	Shorter	Lower	Faster
Open Decortication	Stage III	Longer	Higher	Slower
Conservative (tPA/DNase)	Stage I-II	Variable	High in non-responders	Variable

✶ VATS: Video-assisted thoracoscopic surgery

Table II:

a. Study patients' demographic characteristics data collated: (means, ranges, numbers, % where applicable)
b. Study patient comorbidities collated data (number, %)
c. Study patient presented symptoms collated data

a. DEMOGRAPHIC CHARACTERISTICS		
Age, mean in years (range)	50.6 (36 - 65 years)	
Gender, n (%)	Male 11 (92)	Female 1 (8)
Smoking, n (%)	Smoker 11 (92)	Non-smoker 1 (8)
Body mass index, mean (range)	22.3 (17 - 35.2)	
Laterality, n (%)	Right thorax 6 (50)	Left thorax 6 (50)

a. COMORBIDITIES, n (%)		b. PRESENTING SYMPTOMS, n (%)	
Pulmonary tuberculosis	8 (67)	Dyspnoea	9 (75)
Diabetes mellitus	6 (50)	Chronic cough	7 (58)
Hypertension	2 (17)	Significant unintentional weight loss*	7 (58)
Hepatitis C	2 (17)	Fever	4 (33)
Chronic obstructive airway disease	1 (8)	Anorexia	4 (33)
Autoimmune haemolytic anaemia	1 (8)	Reduced effort tolerance	2 (17)
Ulcerative colitis	1 (8)	Pleuritic chest pain	2 (17)
Lower limb deep vein thrombosis	1 (8)	Pleurocutaneous fistula	2 (17)
Active meliodosis	1 (8)	Night sweats	1 (8)
Metastatic lung adenocarcinoma	1 (8)	Chest swelling	1 (8)
		Headache	1 (8)

✶ Weight loss is considered significant if more than 10% weight loss over a period of 6 months or less

Table III:

(a) Study patients' indications/aetiology collated data
(b) Study patient bacteriology study records collated
(c) Study perioperative parameters data collated (means, ranges, numbers, % where applicable)
(d) Study outcome parameters data collated.

(a) INDICATIONS/ AETIOLOGY, n (%)		(b) BACTERIOLOGY, n (%)	
Empyema thoracis caused by bronchopleural fistula	5 (42)	Tuberculosis	3 (25)
Destroyed lung	5 (42)	Pseudomonas aeruginosa	2 (17)
Recurrent empyema thoracis post decortication	2 (17)	Staphylococcus aureus	1 (8)
(c) PERIOPERATIVE PARAMETERS		Streptococcus pneumoniae	1 (8)
Duration of surgery, mean in minutes (interquartile range)	104.7 (63 - 127)	Klebsiella pneumonia	1 (8)
Blood loss, mean in mls (interquartile range)	366.7 (50 - 400)	Serratia marcescens	1 (8)
ICU/PACU admission post operation, n (%)	3 (25)	Bukholderia pseudomallei	1 (8)
Duration of ICU/ PACU stay, mean in days (range)	2 (1 - 3)	Bukholderia cepacia	1 (8)
Post op ventilation, n (%)	2 (17)	Mixed growth with no predominant colonies isolated	3 (25)
Duration length of stay, median in days (interquartile range)	22.8 (6 - 24)		

(d) OUTCOMES, n (%)	
Resolution of sepsis	11 (92)
Spontaneous closure	8 (67)
Readmission	4 (33)
Premature closure before adequate drainage	3 (25)
Attained closure post revision	3 (25)
Mortality within 30 days	1 (8)
Mortality after 30 days	1 (8)
Malignant lesion	2 (17)

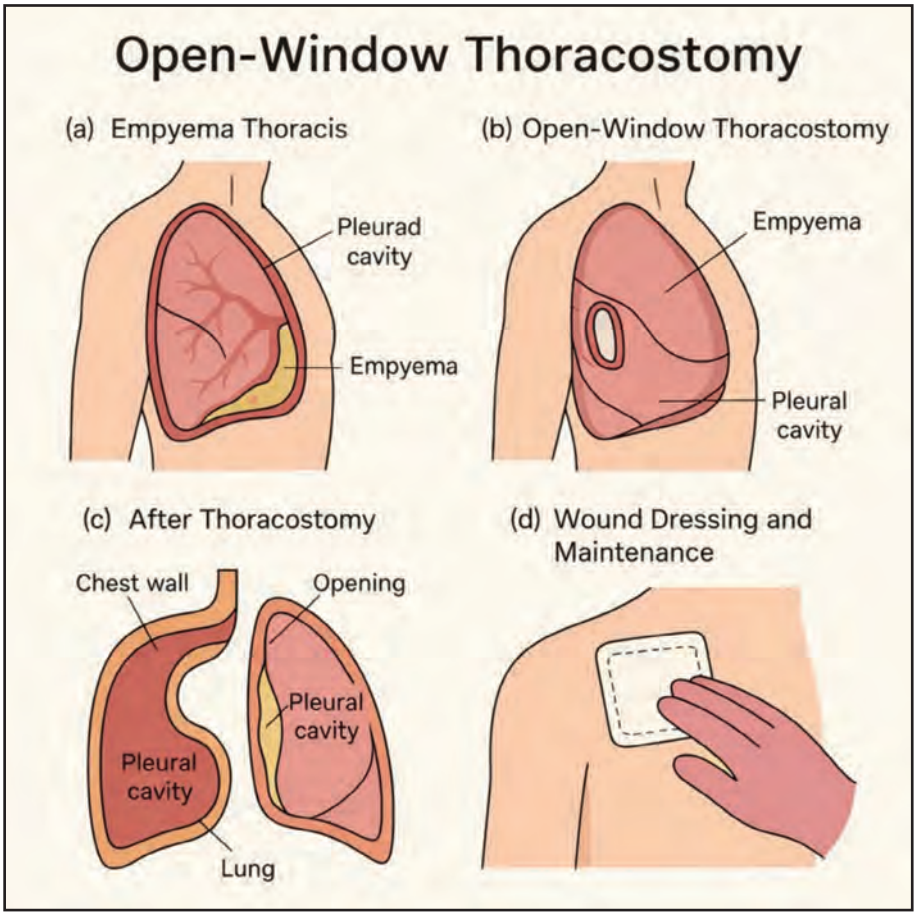

Fig. 1: Sequential anatomical and procedural depiction of OWT

Fig. 2: Spontaneous closure after tuberculous empyema thoracis after 18 months in a 49-year-old male. The previous cavity is closed and almost totally covered by skin. The cosmetic result was acceptable to the patient

sweats, chest swelling and headache seen in one case each. (Table II b.)

OWT was performed for these cases for the following indications: (Table III a.)
1. Empyema thoracis caused by bronchopleural fistula (five patients),
2. Destroyed lung (five patients) and
3. Recurrent empyema thoracis following unsuccessful decortication (two patient).

Bacteriology yielded three patients with tuberculous empyema, six cases of non-tuberculous empyema and mixed growth with no predominant colonies were isolated in three cases. (refer Table III b.) With respect to perioperative parameters (refer Table III c.), duration of surgery ranged from 30 minutes to 240 minutes (mean: 104.7 minutes, interquartile range 63 - 127). Mean blood loss was 366.7mls with range of 50mls to 2000mls and interquartile range from 50 to 400mls. Nine cases were discharged to level one care (general surgical ward) post operatively while three cases required post operative monitoring in level three care; intensive care unit (ICU) or post-operative acute care unit (PACU). Mean duration length of hospital stay was 22.8 days ranging from 4 to 96 days with interquartile range of 6 to 24 days. All cases were extubated postoperatively with the exception of two needed postoperative ventilatory support for two days due to type two respiratory failure and metabolic acidosis secondary to hypovolaemic shock.

In all patients, the septic condition subsided immediately after OWT except in one. There were two mortalities (17%, 95% Confidence Interval: 4.3% – 44.2%). One had bronchopleural fistula post lower bilobectomy for right lung abscess and necrotising pneumonia. Patient succumbed on day 36 post-operation due to unresolved sepsis. The other patient was diagnosed with metastatic lung adenocarcinoma. She received palliative chemotherapy and died 23 days post operation. Three patients developed surgery related complications where blood loss exceeded 750 mLs. There were four (33%, 95% Confidence Interval: 13.6% – 61.2%) cases of readmissions. One case was readmitted after 60 days due to partially treated pneumonia. Three cases were readmitted due to premature closure of OWT before adequate drainage. The aforementioned three cases underwent refashioning to maintain patency. Two cases were diagnosed with metastatic lung adenocarcinoma based on their pleural cortex histopathological examination result and they received palliative chemotherapy. Table III d. displays collated data regarding study patient outcomes. All surviving cases were allowed to heal by secondary intention and cosmetic results were fair and tolerable. (Figure 2) Despite their initial size, all cavities closed spontaneously after periods of between 11 and 22 months. Ten patients survive to date and remain available for further follow-up.

DISCUSSION

OWT remains a cornerstone surgical option for managing chronic, refractory, or complicated empyema thoracis—especially in patients with failed decortication, persistent bronchopleural fistula (BPF), or immunocompromised states. The current retrospective review contributes to this domain by reporting a cohort of 12 patients, predominantly male (92%), with significant infectious comorbidities, notably pulmonary tuberculosis (67%) and diabetes mellitus (50%). This case mix is consistent with other high-burden cohorts from endemic regions.

When juxtaposed against Eloesser flap and Clagett procedure, OWT offers distinct advantages in patients with ongoing contamination, complex fistulae, or necrotic lung tissue. For instance:
- Eloesser flap, which involves creating a long-term pleurocutaneous drainage tract with a skin-lined tunnel, is better suited for frail patients but demonstrates lower spontaneous closure rates (30–40%).
- Clagett procedure, incorporating obliteration of the empyema space with antibiotic irrigation and delayed closure, is superior for sterile, post-pneumonectomy empyema but contraindicated in active infection or residual fistulae as asserted by Clagett OT, Geraci JE.[14]

In this study, the predominant indication for OWT—bronchopleural fistula and destroyed lung (each 42%)—aligns more closely with indications for traditional OWT rather than Clagett, reinforcing its selection here.

The largest OWT review thus far was published by Thourani et al. in 2003 involving 78 patients.[15] The author adopted Modified Eloesser Flap technique in which a U-shaped incision was made to create a flap of skin and subcutaneous tissue over the empyema cavity. The base of the flap is two to four inches wide and lies over the most dependent part of the cavity; its length is two to three inches or equal to the width of two to three ribs and their intercostal spaces. Portions of the two or three ribs just beneath the U-shaped incision are dissected subperiosteally and removed. The soft tissue portion of the chest wall overlying the abscess cavity was then resected completing the unroofing of the empyema cavity. The U-shaped skin flap was reflected onto the most dependent portion of the abscess cavity and sutured to the cavity's floor. The edges of the skin are marsupialised onto the surrounding soft tissue and sterile dressing applied.

In our study, empyema thoracis and its sequelae such as bronchopleural fistula and destroyed lung are more prevalent in the male population. This is attributed to smoking habit as the only non-smoker in our study is a female. The most common immune cell in lung tissue is alveolar macrophage. Alveolar macrophages appear to have multiple functions in the lung. Its primary function is to scavenge particles and remove debris from the lung parenchyma maintaining the sterility of the airway. Smoking habit impairs the function of alveolar macrophages.[16] The author concluded smokers had a higher pulmonary complication rate (19% versus 8%) post thoracotomy and a higher pneumonia rate (11% versus 3%). Patients with tuberculous empyema thoracis are usually underweight with poor nutritional status as a sequalae of catabolic state and chronicity of the disease. On the other hand, obese patients are anticipated to have prolong post operative ventilation due to concomitant obstructive sleep apnoea. However, we did not find body mass index to have any significant

outcome in our series. The only obese patient with body mass index of 35 was extubated immediately post operation with uneventful perioperative recovery.

Three indications for OWT in our study includes empyema thoracis caused by bronchopleural fistula, destroyed lung and recurrent empyema thoracis following unsuccessful decortication. Late presentation or in cases of delayed diagnosis or treatment of pleural infection can lead to spontaneous drainage of pus through the bronchial tree resulting in bronchopleural fistula. Airway commensal contaminates the sterile pleural space, and this results in a vicious circle and rapid spread of infection throughout the whole pleural space. Air leak results in residual pleural space and persistent empyema. OWT is performed in most patients with empyema thoracis caused by bronchopleural fistula since closed drainage fails to achieve control of a permanently contaminated space. Likewise, as asserted by Halezeroglu S, Keles M, Uysal A, et al., destroyed lung most often would require OWT and is characterised by total and irreversible destruction of one lung due to chronic bronchopulmonary infections.[17] Most common causes are tuberculosis, aspergilloma, idiopathic bronchiectasis, and recurrent pneumonia. Radiological findings typically show a very small and fibrotic lung tissue, mediastinal displacement, and compensatory enlargement of the contralateral lung. Asymptomatic patients are followed up conservatively, while frequent bronchopulmonary infections and empyema requires OWT considering the destroyed lung parenchyma fails to expand leaving a potential pleural space. Recurrent empyema thoracis after decortication is another indication of note for OWT. In such cases, re-decortication is no longer feasible and a large part of the pleural cavity contain necrotic debris which for practical reasons cannot be removed. The lungs are thus not stabilised against collapse.

The bacteriology data show Mycobacterium tuberculosis (25%) as the leading isolate, with diverse Gram-negative and opportunistic pathogens (e.g., *Pseudomonas aeruginosa, Burkholderia pseudomallei*), further substantiating the selection of OWT for complex and potentially relapsing infections. The presence of such organisms precludes early wound closure and demands sustained drainage—a clear advantage of the open technique over sealed irrigation approaches. Pseudomonas aeruginosa infection require the presence of neutrophils for elimination. Similarly, tuberculosis is resistant to alveolar macrophages especially in primary tuberculosis. In most individuals, the host immune response contains the infection within a few weeks, leaving a small granuloma that may calcify over time (Ghon lesion). However, in patients who cannot contain the initial infection because of impaired host immune system, poor nutrition, or in extremes of age, the infection may progress leading to lung injury and dense pleural adhesions. Chronic tuberculous empyema is frequently complicated by bronchopleural fistula, leading to a mixed empyema or complicated tuberculous pleural effusion, characterised by contamination with both mycobacterium tuberculosis and common pyogenes. As soon as empyema is confirmed, adequate drainage should be instituted. In this setting, our preference is OWT.

In our review, there is a wide range of duration of surgery (30 minutes to 240 minutes, interquartile range 63 - 127). One possible explanation for this might be due to an unforeseen intraoperative finding. Given that we are aware of the presence of bronchopleural fistula or destroyed lung hence, OWT is unavoidable, the duration of the surgery will be relatively short. On the contrary, a failed attempt at decortication (to achieve lung expansion) will invariably lead to extended duration of surgery.

In this series, spontaneous closure of the thoracostomy wound was achieved in 67% (95% Confidence Interval: 35.4% – 87.9%) of patients, with resolution of sepsis occurring in 92% (95% Confidence Interval: 62.1% – 99.6%). This aligns closely with published data by Regnard et al. (2000), who reported spontaneous closure in approximately 60% of cases, albeit over extended follow-up (median: 9 months).[18]

Importantly, this study reported a low incidence of prolonged postoperative ventilation (17%) and relatively modest perioperative blood loss (mean: 366.7 mLs), reflecting the procedural safety in experienced hands. Three complications were encountered in our practice in which blood loss exceeds 750mls. This value was used as the cut off limit for excessive blood loss as this reflects more than 15% of adult total blood volume beyond which there will be failure of normal compensatory physiologic response.[19] These were due to large diaphragmatic tear in two cases and one liver laceration. These patients received immediate adequate intraoperative fluid and blood resuscitation and no adverse event directly related to the blood loss was observed. Although our mortality rate was higher than the results published by Thourani et al. (17% vs 5%) this does not reflect the actual situation considering our smaller sample size (12 patients vs 78 patients).[15]

This series' findings are consistent with global retrospective OWT series from tuberculosis-endemic or low-resource settings. However, limitations such as small sample size and retrospective design preclude definitive comparative effectiveness conclusions.

Nevertheless, the high sepsis resolution rate (92%), substantial spontaneous closure proportion (67%), and relatively low morbidity affirm OWT as a viable and effective option in carefully selected patients, especially those with complex infections not amenable to flap closure or primary thoracoplasty.

CONCLUSIONS

OWT is an effective method for rapid control of severe life-threatening septic conditions. It is suitable even in severe cases of empyema thoracis with very low operative risk. Postpneumonectomy empyema and empyema in sick, elderly patients in whom drainage techniques have failed and who would not tolerate the stress of a decortication procedure responded most favourably.

The main shortcoming of the method, however, is the resulting granulating defect which necessitates either surgical correction or prolonged conservative treatment with the need for a long hospital stay in some cases.

This latter fact will certainly reduce the quality of life in cancer patients in whom recurrence or progression of the underlying malignancy is present. In these patients, OWT should remain the last option.

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ETHICAL APPROVAL

This study has been approved by the National Medical Research Register of Malaysia on 20th of February 2024 (NMRR ID: NMRR ID-23-03712-F80)

CONFLICT OF INTEREST

None.

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ORIGINAL ARTICLE

Custodial HTK Cardioplegia in conventional cardiac surgery: A retrospective analysis From UiTM

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ABSTRACT

Introduction: Custodial-HTK (Histidine-Tryptophan-Ketoglutarate) solution and blood cardioplegia are both established methods for myocardial protection during cardiac surgery. However, their utility in patients undergoing complex cardiac surgery is not extensively study. This study compares clinical outcomes between patients receiving Custodial-HTK and blood cardioplegia in one of the tertiary Malaysian cardiac center.

Materials and Methods: We retrospectively analyzed data from 79 patients who underwent elective, on-pump, cross-clamp cardiac surgeries at Faculty of Medicine, Universiti Teknologi MARA (UiTM) from August 2022 to July 2023. Patients undergoing emergency procedures, off-pump, or incomplete records were excluded. Patients receiving Custodial-HTK were typically those with impaired LVEF or requiring complex surgeries.

Results: Custodial-HTK was used in 12% of cases. These patients had slightly higher mean age (61.9 ± 7.6 vs. 59.9 ± 8.8 years) and higher mean EuroSCORE II, although the latter was not statistically significant (p = 0.115). Comorbidities including diabetes, hypertension, stroke, and renal disease were comparable between groups. The Custodial group showed significantly lower mean LVEF (43.7 ± 14.7%) and greater use of pre-induction intra-aortic balloon pump (IABP) (20%). Complex procedures were more frequent (50%), with longer mean cardiopulmonary bypass (181.7 ± 65.1 minutes) and cross-clamp durations (131.3 ± 50.4 minutes). Despite these differences, postoperative complication rates, ICU stay, total hospital stay, and 30-day mortality did not differ significantly between groups.

Conclusion: Although patients receiving Custodial-HTK had higher surgical complexity and poorer baseline cardiac function, postoperative outcomes were within acceptable clinical range to the blood cardioplegia group. These findings support the use of Custodial-HTK as a safe and effective alternative in high-risk cardiac surgery patients.

KEYWORDS:
Custodial HTK solution; cardioplegia; myocardial protection; cardiac surgery; blood cardioplegia; clinical outcomes

INTRODUCTION

Myocardial protection is pivotal in cardiac surgery, preserving the myocardium during periods of ischaemia that normally encounter during cardiopulmonary bypass.[1] Myocardial protection during cardiopulmonary bypass relies primarily on two key strategies: hypothermia[2], which reduces myocardial oxygen demand, and potassium-induced electromechanical arrest, which halts the heart's electrical and mechanical activity to prevent energy depletion.[3]

Although blood cardioplegia remains a standard myocardial protection strategy in cardiac surgery, Custodiol-HTK—a single-dose, crystalloid cardioplegia—has gained increasing acceptance for its prolonged protective effect and simplified delivery, allowing an uninterrupted operative field.[4] In smaller cardiac centers such as ours, managing complex or high-risk cases, particularly in patients with significantly reduced ejection fraction, poses substantial challenges. With limited resources and intra-aortic balloon pump (IABP) support as the only available mechanical circulatory device, the extended duration of myocardial arrest afforded by Custodiol-HTK offers practical advantages by reducing interruptions and facilitating operative efficiency. Moreover, its biochemical properties provide reliable myocardial protection during lengthy or technically demanding procedures. Despite these advantages, evidence regarding its performance in high-risk populations, including those with low LVEF or requiring IABP support which remains limited. Therefore, this study aims to evaluate the perioperative outcomes associated with Custodiol-HTK compared with traditional blood cardioplegia within our institution.

MATERIALS AND METHODS

The authors conducted an observational cohort study was conducted in all patients undergoing an elective, conventional cardiac surgery, using an on-pump and cross-clamp techniques. The study was conducted at the Cardiovascular and Thoracic Department, Faculty of Medicine, Universiti Teknologi Mara (UITM).

This study includes cohort of patients from August 2022 to July 2023. Patients who underwent as emergency or urgent surgery, patients with off-pump and on-pump beating heart techniques, and patient with incomplete records were excluded in this study.

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The decision to use Custodiol-HTK cardioplegia was made collaboratively by the operating surgeon, perfusionist, and attending anesthesiologist. In our institution, Custodiol-HTK is preferentially selected for patients with poor left ventricular systolic function, defined as a left ventricular ejection fraction (LVEF) <40%, or for complex cardiac procedures, which we defined as operations involving two or more concomitant interventions. In Coronary Artery Bypass Grafting patient, poor coronary targets were not classified as complex, as no standardized SYNTAX scoring was performed to objectively assess coronary anatomical complexity. All remaining patients received our institution's standard myocardial protection strategy using conventional blood cardioplegia. For analysis, patients were categorized into two groups: Group 1, consisting of those who received Custodiol-HTK, and Group 2, comprising patients who received standard blood cardioplegia.

Data Collection and Analysis: Data on patient demographics, comorbidities, intraoperative variables, and postoperative outcomes were collected for analysis. Group comparisons were performed using the Independent t-test for continuous variables and the Chi-square test for categorical variables. A two-tailed p-value of <0.05 was considered statistically significant.

Primary outcome of this study is to compare the 30-day Mortality between each group, whereas the secondary outcome will be mean duration of ICU stay, mean duration of hospital stay and also post-operative complications such as postoperative arrhythmias, mediastinal bleeding, renal failure, pulmonary complication, post-operative stroke, transaminitis, new heart failure and surgical site infection.

RESULTS

Patient Demographics and Baseline Characteristics

This study was conducted at UiTM from August 2022 to July 2023. A total of 79 patients were assessed retrospectively and the elegibility criteria includes electives patients on conventional on-pump, cross-clamp cardiac surgery. Exclusion criteria were emergency cardiac surgeries, as well as off-pump surgeries and on-pump beating heart surgeries where cardioplegia is not used in these 2 methods. Out of these 79 patients, 10 patients received Custodial-HTK solution as cardioplegic myocardial protection, whereas the other 70 patients received conventional blood cardioplegia.

Mean age was 61.9 ± 7.6 years in the Custodiol group and 59.9 ± 8.8 years in the blood cardioplegia group. The 95% confidence interval for the between-group difference ranged from –7.83 to 3.85, with no significant difference observed (p = 0.493). Male gender is more prevalent in Custodial group (90.0% vs 79.9%). EuroSCORE II was higher in the Custodiol group (2.39) compared with the blood cardioplegia group (1.44), with a 95% confidence interval for the mean difference ranging from –1.77 to –0.14 (p = 0.115), although the difference was not statistically significant. Mean ejection fraction was significantly lower in the Custodiol group (43.7) compared with the blood cardioplegia group (49.09), with a 95% confidence interval for the mean difference of –1.2 to 11.7 (p = 0.001), with 50% of the Custodial group cohort have EF less than 40% (p value: 0.006). Requirement of IABP preinduction was seen statistically higher in the Custodial group (20.0% vs 1.44%, p = 0.041) as compared to the Blood group.

There were no significant differences in NYHA or CCS class, nor in prevalence of diabetes, hypertension, smoking, renal disease, stroke, or left main disease between the 2 groups. On the hand, Custodial group have shown to have numbers of patient requiring inotrope preinduction and history of Cardiogenic shock although it does not achieve statistical significant.

Intraoperative Data

More than 90% patient in Blood group underwent isolated CABG, with only 1.4% from the cohort underwent double valve procedure, compared to Custodial group which only 50% of the cohort underwent isolated CABG while the other 50% underwent more complex procedures such as double valve procedures and CABG with valve procedures. In regard to cardiopulmonary bypass (CPB) and aortic cross-clamp durations, patients in the Custodial group had significantly longer CPB time (181.7 ± 65.1 minutes; 95% CI: –78.01 to –24.87) and cross-clamp time (131.3 ± 50.4 minutes; 95% CI: –56.76 to –16.28) compared to the Blood group, achieving statistical significance (p < 0.001). This finding is expected, as Custodial solution is more commonly used in patients undergoing more complex surgical procedures.

Postoperative Outcomes

Primary outcome of 30- day mortality is similar in both Custodial and Blood group (10.00 vs 10.14, p value: 0.734). For the secondary outcome, the mean duration of ICU stay was similar between the Custodial and Blood groups (6.42 ± 6.81 vs. 6.90 ± 4.40 days; 95% CI: –4.91 to 3.95), with no statistically significant difference (p = 0.973). The Custodial group recorded a shorter mean duration of hospital stay compared to the Blood group (8.9 ± 5.5 vs. 10.67 ± 9.44 days); however, this difference was not statistically significant (p = 0.708), with a 95% confidence interval of –4.34 to 7.88. For the post-operative complications outcome such as arrhythmias, renal failure, pulmonary complication, transaminitis and new onset of heart failure is higher in the Custodial group, however it was statistically not significant.

DISCUSSION

This retrospective study presents our early institutional experience with the use of Custodiol-HTK solution as a cardioplegic agent, compared to conventional blood cardioplegia, as part of the myocardial protection strategy. In our centre, blood-based cardioplegic solutions such as St. Thomas' extracellular cardioplegia and Del Nido cardioplegia are routinely employed to achieve myocardial protection during cardiac surgery. Both solutions have demonstrated excellent myocardial preservation by inducing diastolic arrest during aortic cross-clamping.

The St. Thomas' cardioplegic solution, first introduced in 1976, is an extracellular, potassium-based formulation designed to induce rapid and sustained myocardial arrest. In 1981, the solution was modified by increasing its potassium

Table I: Baseline Characteristics, Demographic and Preoperative Variables

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Age, mean (SD)	59.9 ± 8.805	61.9 ± 7.62	0.439	(-7.83, 3.85)
Male (%)	79.70	90.00	0.392	
Euroscore, mean (SD)	1.44 (1.14)	2.39 (1.67)	0.115	(-1.77, -0.14)
MI < 90 days (%)	52.17	30.00	0.166	
Diabetic (%)	55.07	50.00	0.512	
Smoking (%)	49.27	30.00	0.213	
Hypertension (%)	84.05	90.00	0.528	
Dyslipidemia (%)	62.31	60.00	0.573	
Renal Disease (%)	26.08	20.00	0.510	
Stroke (%)	2.89	0	0.759	
Sinus Rhythm (%)	95.65	80.00	0.78	
LM Disease (%)	43.47	40.00	0.558	
EF Good >50% (%)	52.00	50.00	0.006	
EF Moderate 40-49% (%)	34.80	0	0.006	
EF Impaired <40% (%)	13.00	50.00	0.006	
EF Mean (SD)	49.09 ± 8.89	43.7 ± 14.7	0.001	(-1.2, 11.7)
Inotropes Pre-Induction (%)	0	10.00	0.127	
Cardiogenic Shock (%)	4.34	10.00	0.425	
IABP Preinduction (%)	1.44	20.00	0.041	

Table II: Intraoperative Variables

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Isolated CABG (%)	92.75	50.00	<0.001	
Single Valve Procedure (%)	2.89	0	<0.001	
CABG + Valve Procedure (%)	0	40.00	<0.001	
Double Valve/Other (%)	1.44 / 2.89	10.00 / 0	<0.001	
2 Grafts (%)	17.18	22.22	0.896	
3 Grafts (%)	67.18	66.66	0.896	
4 Grafts (%)	15.62	11.11	0.896	
CPB Time, mean (SD)	130.26 ± 34.64	181.70 ± 65.12	<0.001	(-78.01, -24.87)
Aortic Cross Clamp Time, mean (SD)	94.78 ± 26.18	131.3 ± 50.43	<0.001	(-56.76,-16.28)

Table III: Postoperative Outcomes

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Arrhythmias (%)	18.84	40.00	0.209	
Mediastinal Bleeding (%)	13.04	0	0.594	
Renal Failure (%)	15.94	30.00	0.377	
Pulmonary Complication (%)	31.88	40.00	0.722	
Post-op Stroke (%)	4.35	0	0.663	
Transaminitis (%)	18.84	30.00	0.415	
New Heart Failure (%)	4.34	10.00	0.425	
Surgical Site Infection (%)	14.49	0	0.345	
30-day Mortality (%)	10.14	10.00	0.734	
ICU Stay, mean (SD)	6.42 ± 6.81	6.9 ± 4.4	0.973	(-4.91, 3.95)
Duration of Hospitalization, mean (SD)	10.67 ± 9.44	8.9 ± 5.5	0.708	(-4.34, 7.88)

concentration and reducing its sodium content to enhance myocardial protection. The modified St. Thomas' solution remains widely used in contemporary cardiac surgery, providing effective myocardial protection with a recommended redosing interval of approximately 20 minutes.[7]

The Del Nido cardioplegic solution was developed in the 1990s by Dr. Pedro Del Nido. It is an extracellular crystalloid solution formulated with Plasma-Lyte as the base, supplemented with magnesium sulfate, sodium bicarbonate, potassium chloride, and lidocaine. In contrast to the St. Thomas' solution, Del Nido cardioplegia provides prolonged myocardial protection, allowing a single dose to maintain electromechanical arrest for up to 90 minutes.[8]

Custodiol-HTK solution is a widely used crystalloid cardioplegia developed originally for organ preservation in 1970s.[6] Custodial-HTK is intracellular-type cardioplegic solution that induces diastolic arrest primarily through hyperpolarization, achieved by its low sodium and calcium composition.[4,5]

Custodial-HTK solution formulation reduces intracellular calcium overload, thereby minimizing ischemia-induced cellular injury. Histidine acts as a buffer to maintain acid-base balance, tryptophan stabilizes cell membranes, ketoglutarate serves as a metabolic substrate to support ATP regeneration, and mannitol reduces edema and scavenges free radicals.[5] Together, these components provide prolonged myocardial protection with a single-dose administration, often effective for up to 2 hours, making it especially useful in complex or prolonged cardiac surgeries unlike blood cardioplegia which need to be administered repeatedly every 15-30 minutes.[5] The extended duration of myocardial protection provided by Custodiol-HTK solution minimizes the need for repeated dosing, thereby preventing intraoperative interruptions and offering particular advantages in complex cardiac procedures.

In this study, patients who received Custodiol-HTK cardioplegia demonstrated a shorter duration of hospital stay compared to those in the blood cardioplegia group; however, the difference did not reach statistical significance. Postoperative complications, including arrhythmias, renal dysfunction, pulmonary complications such as prolonged mechanical ventilation and extended oxygen dependency, postoperative transaminitis, and new-onset heart failure, were observed more frequently in the Custodiol group, although these differences were not statistically significant. The underlying cause for the increased incidence of postoperative arrhythmias associated with Custodiol-HTK cardioplegia remains uncertain. Our findings are consistent with those reported by Saber et al., who also observed a higher incidence of postoperative ventricular fibrillation in patients receiving Custodiol HTK compared with blood cardioplegia.[9]

Other perioperative outcomes, such as the duration of ICU stay, were no significance difference between the two groups. However, the total length of hospital stay and 30-day mortality were shorter in the Custodiol-HTK group, although these differences did not reach statistical significance. Similar findings were reported by Ihab Ali et al., who observed shorter ICU and hospital stays in patients undergoing various cardiac surgical procedures using Custodiol HTK compared to blood cardioplegia.[10]

Our findings indicate that Custodial-HTK is a viable myocardial protection strategy, even in high-risk patients with impaired LV function or requiring IABP support. Despite longer operative times and more complex surgeries, outcomes were no significant difference to the standard blood cardioplegia group. This study has several limitations. The sample size of the Custodiol-HTK group was relatively small, which may limit the statistical power to detect significant differences between groups. Furthermore, the retrospective study design inherently restricts the ability to establish causal relationships.

Another important limitation is that propensity score matching could not be performed due to the very low number of patients in the Custodial group and the substantial imbalance in baseline characteristics between the two cohorts. Attempting to match these groups would have further reduced the sample size, resulting in inadequate statistical validity. Additionally, the cost of Custodiol-HTK represents a practical limitation in its wider adoption, as it is considerably more expensive compared to conventional blood cardioplegia. Future randomized controlled trials with larger sample sizes are warranted to better evaluate and optimize the clinical outcomes associated with Custodiol-HTK compared with blood cardioplegia.

CONCLUSION

In this retrospective experience from UiTM, Custodial-HTK cardioplegia was used predominantly in patients with more complex cardiac pathology and higher preoperative risk profiles, including reduced ventricular function and greater need for mechanical or inotropic support. Despite these higher-risk characteristics and longer operative durations typically associated with complex procedures, postoperative outcomes including 30-day mortality, ICU stay, hospital stay, and major postoperative complications, remained within clinically acceptable range to expected standards of care.

These findings suggest that Custodial-HTK can be used safely and effectively as a myocardial preservation strategy in selected higher-risk or complex surgical cases. Further prospective studies with larger cohorts are warranted to strengthen these observations and better define the optimal role of Custodial-HTK in contemporary cardiac surgery practice.

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ORIGINAL ARTICLE

Prevalence and factors associated with seizures among patients with infective encephalitis

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ABSTRACT

Introduction: Seizures are a common and clinically significant complication of infective encephalitis, often associated with greater disease severity and poorer neurological outcomes. Identifying reliable clinical and diagnostic predictors of seizures is critical to improve early risk stratification and guide targeted management. However, regional data on the seizure prevalence and associated factors in encephalitis remain limited. This study aims to determine the prevalence, clinical characteristics, and risk factors associated with seizure occurrence in patients with infective encephalitis admitted to a tertiary care centre in Malaysia.

Materials and Methods: We conducted a retrospective observational study involving 173 patients diagnosed with infective encephalitis and admitted to a tertiary referral hospital. Data on demographics, clinical presentation, Glasgow Coma Scale (GCS) scores, electroencephalography (EEG), neuroimaging, and cerebrospinal fluid (CSF) parameters were extracted from medical records. Seizure occurrence and characteristics were analysed. Statistical analyses included univariate and multivariate logistic regression to identify independent predictors of seizures. Missing data for selected variables were imputed using median substitution based on the distribution of available data.

Results: Seizures were reported in 55.5% of patients (n=96), with generalised seizures being more common than focal. EEG abnormality emerged as the most significant independent risk factor for seizure occurrence (aOR 5.22, 95% CI 2.22–12.26, p <0.001). Altered behaviour (aOR 0.22, 95% CI 0.11-0.45, p < 0.001) and elevated CSF protein (OR 0.44, 95% CI 0.20–0.95, p = 0.036) were significantly associated with lower odds of seizures. Functional outcomes at discharge (assessed by Glasgow Outcome Scale), showed that higher seizure burden, particularly status epilepticus (p<0.001) and increased seizure frequency (p=0.008) was significantly associated with poorer recovery at discharge.

Conclusion: This study confirms the substantial clinical burden of seizures in infective encephalitis and highlights the need to prioritise systemic risk stratification in routine care. EEG abnormality is the strongest independent predictor of seizure risk and should be incorporated into early diagnostic evaluation for risk stratification. Early EEG monitoring, timely antiseizure management, and structured neurological assessment are critical to mitigate secondary brain injury and optimise outcomes.

KEYWORDS:
Infective encephalitis; seizures; risk factors; Malaysia

INTRODUCTION

Encephalitis, defined as inflammation of the brain parenchyma accompanied by neurologic dysfunction, arises from direct central nervous system (CNS) infection or immune-mediated mechanisms.[1,2] Globally, the incidence of clinically diagnosed encephalitis ranges from 3.5 to 7.4 cases per 100,000 population annually. The age-standardized incidence rate of encephalitis was found to be higher in low-middle regions, reaching 31.63/100,000 in 2019. The incidence of encephalitis was 5.23/100,000 in England compared to 185/100,000 in Nepal during an outbreak of Japanese encephalitis.[3,4] The aetiological spectrum is broad, encephalitis can be divided into infective and non-infective encephalitis including autoimmune disorders and paraneoplastic syndromes.[5,6] Differential diagnoses include metabolic encephalopathies, CNS neoplasms, and vasculitis, necessitating meticulous clinical and laboratory evaluation.[7]

The most common symptoms in encephalitis include acute or subacute mental state changes, fever, headache, focal neurological deficits, and seizures.[1,5] The consensus case definition incorporates altered mental status lasting ≥24 hours, accompanied by at least two of the following: fever ≥38°C within 72 hours of presentation, seizures not attributable to a known seizure disorder, new-onset focal neurological signs, cerebrospinal fluid (CSF) pleocytosis (white blood cell count ≥5/mm³), neuroimaging abnormalities, or electroencephalogram (EEG) findings consistent with encephalitis.[1]

Seizures represent a frequent and critical complication, reflecting severe neurological injury and often correlating

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with impaired consciousness, abnormal neuroimaging, and EEG changes.2,8 The International League Against Epilepsy (ILAE) defines acute symptomatic seizures as those occurring within seven days of a CNS insult.[9] Reported seizure incidence in encephalitis varies from 2% to 67%, depending on aetiology and study design.[2,10] In one clinical cohort, approximately one-third of encephalitis patients experienced seizures during hospitalisation.[11]

Seizure occurrence signals greater disease severity, complicates management and portends poorer outcomes, including prolonged hospitalisation, increased intensive care requirements, and an elevated risk of long-term sequelae such as post-encephalitic epilepsy (PEE).[2,8] Evidence suggests that patients who have had an acute seizure are more likely to develop chronic epilepsy. Longitudinal studies indicated that patients with acute seizures post-encephalitis have a substantially higher 20-year risk of developing epilepsy following viral encephalitis (22%) compared to those without seizures (10%).10 Development of PEE necessitates prolonged antiseizure therapy and is associated with diminished functional independence and quality of life.[10,12,13]

Despite advancements in diagnostics and therapeutics, encephalitis remains a leading cause of morbidity and mortality worldwide, with fatality rates ranging from 5.6% to 39.3%.[6] Persistent neurological impairments, including memory loss, behavioural disturbances, fatigue, and recurrent seizures, contribute to long-term disability.[13] Notably, the epidemiology and clinical profile of seizures in encephalitis within South East Asia remain insufficiently characterised. This region harbours distinct viral aetiologies, such as Japanese encephalitis virus (JEV), which is the predominant cause of encephalitis.[14] However, comprehensive, harmonized data on seizure prevalence, risk factors, and outcomes in encephalitis across South East Asia are scarce, partly due to heterogeneous diagnostic capabilities and limited prospective studies. This paucity of data hampers effective risk stratification, targeted management and public health interventions. Addressing this critical knowledge gap, our study aims to systematically evaluate the prevalence, clinical characteristics and correlates of seizure occurrence in patients with infective encephalitis admitted to a tertiary health care centre in South East Asia.

MATERIALS AND METHODS

Study design and population

This was a single-centre, retrospective study, conducted at Hospital Canselor Tuanku Muhriz (HCTM), a tertiary academic hospital in Malaysia. The study population consisted of adult patients (aged 18 years or older) admitted with a clinical diagnosis of infective encephalitis between 1st January 2016 and 31st May 2025. Ethical approval was obtained through the local Ethics and Research Board (JEP-2023-519).

The diagnosis of infective encephalitis was based on clinical, laboratory, and radiological criteria, following the International Encephalitis Consortium definition: altered mental status lasting ≥24 hours without an alternative cause, accompanied by at least two of the following—fever ≥38°C within 72 hours of presentation, seizures not attributable to a pre-existing seizure disorder, new-onset focal neurological signs, CSF pleocytosis (white cell count ≥5/mm³), brain imaging suggestive of encephalitis, or EEG abnormalities consistent with encephalitis.[1] Seizures were classified as acute symptomatic seizures if they occurred within seven days of encephalitis onset, following the International League Against Epilepsy (ILAE) definition.[9]

Patients with autoimmune encephalitis, prior stroke, traumatic brain injury, brain tumour, previous neurosurgery, or other chronic neurological disorders unrelated to encephalitis were excluded.

Data collection

Eligible patients were identified through hospital medical records and infectious disease registries. With assistance from the medical records department, relevant data were manually extracted and entered into a data collection form. Variables collected included demographic details (age, sex, ethnicity), clinical characteristics (fever, headache, altered behaviour, Glasgow Coma Scale [GCS] score, and seizure occurrence), comorbidities (e.g., diabetes mellitus, hypertension, tuberculosis), CSF parameters (protein, glucose, pleocytosis, and culture results), EEG and neuroimaging findings, seizure type and frequency, and antiseizure medication use. Patients were subsequently categorised into two groups based on the presence or absence of seizures.

Sample size

Sample size estimation was performed for both prevalence and comparative analyses.

$$n = \left[\frac{Z}{\Delta}\right]^2 p(1-p)$$

n : required sample size
p : prevalence from previous study (Annegers et al)(10)
Z : 1.96 for 95% confidence interval
Δ : absolute precision = 0.05

Assuming p = 0.068 (6.8% prevalence from Annegers et al(10) with Z = 1.96 (95% CI) and Δ = 0.05, the calculated sample size was 97 patients

For comparative analysis of risk factors, the sample size was calculated using the formula for two-proportion described by Rosner's method.(15)

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \, \delta^2}{d^2}$$

N : sample size per group
Zα/2 : 1.96 for 95% confidence
Zβ : 0.84 for 80% power
δ : standard deviation
d : clinically meaningful difference between group means

Based on data from Granerod et al.,[16] which identified 203 patients with encephalitis, with 42% attributed to infectious causes and 21% to immune-mediated aetiologies, a minimum of 73 patients per group was required. Allowing for a 10% dropout rate, the final estimated sample size was 81 per group, totalling 162 patients.

Statistical Analysis
Data were analysed using 'Statistical Product and Service Solution' (SPSS), Version 30. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means ± standard deviation or medians (25th, 75th percentile) depending on normality of distribution.

Statistical analyses included both descriptive and inferential methods. Univariate analyses were performed to describe the profiling of the samples and bivariate analyses were performed to assess associations between independent variables and seizure occurrence using Pearson's Chi square. Variables that were statistically significant in the bivariate analysis, as well as those considered clinically relevant, were included in the multivariate logistic regression model to identify independent predictors of seizure occurrence after adjusting for confounding factors. Results from binary logistic regression are presented as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and p-values. Statistical significance was set at $p < 0.05$.

Missing Data Management:
Missing data were identified in 8.7% of CSF parameters, 5.9% of EEG data, and 1.2% of neuroimaging findings. To address missing data and minimise potential bias, imputation was performed using the median for continuous variables (CSF protein = 489 mg/dL; CSF glucose = 3.75 mmol/L) and the most frequent category for categorical variables (CSF culture = "no growth," EEG = "normal," neuroimaging = "normal"). This single-imputation approach was chosen to maintain the overall distribution of variables for analysis, provided that the proportion of missing data did not exceed 10% for each variable.

RESULTS

Descriptive Statistics
205 patients with presentation of encephalitis were screened for this study. Eventually, 173 participants diagnosed with infective encephalitis were recruited in the study. The mean age was 46.8 years (SD ± 20) with a slight male predominance (n=96, 55.5%). Seizures were reported in 96 participants (55.4%), predominantly affecting young adults aged 18–44 years.

Hypertension (n=54, 31.2%) and diabetes mellitus (n=45, 26.0%) were the most frequently reported comorbidities. Both conditions were slightly more prevalent in the non-seizure group. No significant differences were observed between groups for other comorbidities, including dyslipidaemia, ischaemic heart disease, tuberculosis, HIV, or psychiatric disorders.

Fever was the most frequently reported presenting symptom (n=108, 62.4%), followed by altered behaviour (n=90, 52%) and headache (n=48, 27.7%). Fever was slightly more common among patients with seizures (n=57, 59.4%), whereas altered behaviour was predominantly observed in those without seizures (n=54, 70.1%). Lethargy and focal motor weakness were infrequent across the cohort. The median GCS score at presentation was 14 (11,15). The majority of patients (n=159, 91.9%) presented with GCS 10–15, while a lower GCS of 3–9 was seen more frequent in the seizure group (n= 12, 12.5%) than in the non-seizure group (n=2, 2.6%).

CSF analysis was available for 158 patients. Positive CSF culture growth was detected in 40 cases (23.1%), with viral pathogens being the most frequently isolated (20, 11.6%), followed by bacterial (n=5, 2.9%), Toxoplasma (n=3, 1.7%) and Cryptococcal organisms (2, 1.2%). Biochemical abnormalities such as elevated protein levels >400 mg/L was identified in 95 cases (54.9%), and low glucose levels <2.22 mmol/L in 18 cases (10.4%). Elevated CSF protein was more frequent in the seizures group (n=48, 50.0%), while low CSF glucose levels were slightly more prevalent in the non-seizure group (n=9, 11.7% vs. n=9, 9.4%). CSF pleocytosis (WBC ≥5/mm³) was infrequent (n=9, 5.2%) and showed no significant difference between the two groups.

Abnormal neuroimaging was noted in 86 patients (49.7%), more commonly among those with seizures (n=52, 54.2%). EEG was performed in 163 patients, revealing abnormal findings in 109 (63.0%), significantly more frequent in the seizure group (n=71, 74.0% vs. n=38, 49.4%). Among the 96 seizure patients, generalized seizures were more common (n=70, 72.9%) compared to focal seizures (n=26, 27.1%). Status epilepticus occurred in 26 patients (27.1%). Seizure onset was typically early in the clinical course, with a median time of 1 day (0,2) following initial presentation of encephalitis symptoms. Most patients experienced infrequent seizures; only 13 (7.3%) reported five or more episodes per month.

Antiseizure medications were prescribed in 73 seizure patients (76.0%), most of whom received monotherapy (n=53, 55.2%), while 20.8% received polytherapy. The overall treatment burden was low, with a median number of antiseizure medications of 0 (0, 1).

Functional outcomes of patients at discharge were assessed using Glasgow Outcome Score (GOS), score (Table II). Majority of patients (n = 130, 75.1%) achieved good recovery, while 15 (8.7%) had severe disability, 12 (6.9%) had moderate disability, 2 (1.2%) remained in a neurovegetative state, and 14 (8.1%) died. The distribution of GOS score did not differ significantly between seizure and non-seizure groups ($p = 0.165$).

Patients who developed status epilepticus was significantly associated with poorer outcomes ($p < 0.001$), including higher rates of death (n=4/26, 15.4%) and severe disability (n= 7/26, 26.9%) compared with those without status epilepticus. Similarly, increasing seizure frequency was significantly associated with worse functional outcomes at discharge ($p = 0.008$; linear-by-linear association $p = 0.048$). In contrast, seizure type (focal vs. generalised) showed no significant association with GOS score ($p = 0.287$). In summary, while seizure occurrence alone did not significantly influence overall outcome, the occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes.

Table I: Sociodemographic, clinical characteristics and investigation parameters of study participants with seizure presentation

Demographic/Clinical characteristics	Total (N=173)	No seizure (N=77)	With seizure (N=96)	p-value
Age group, n (%)				0.500 [a]
18 – 44	89 (51.4)	37 (48.1)	52 (54.2)	
45 – 64	40 (23.1)	21 (27.3)	19 (19.8)	
65 and above	44 (25.4)	19 (24.7)	25 (26.0)	
Gender, n (%)				0.823 [a]
Male	96 (55.5)	42 (54.5)	54 (56.3)	
Female	77 (44.5)	35 (45.5)	42 (43.6)	
Race, n (%)				0.786 [a]
Malay	96 (55.5)	41 (53.2)	55 (57.3)	
Chinese	55 (31.8)	27 (35.1)	28 (29.2)	
Indian	13 (7.5)	6 (7.8)	7 (7.3)	
Others	9 (5.2)	3 (3.9)	6 (6.3)	
Concomitant diseases, n (%)				
Hypertension				0.328 [a]
Yes	54 (31.2)	27 (35.1)	27 (28.1)	
No	119 (68.8)	50 (64.9)	69 (71.9)	
Diabetes mellitus				0.735 [a]
Yes	45 (26.0)	21 (27.3)	24 (25.0)	
No	128 (74.0)	56 (72.7)	72 (75.0)	
Dyslipidaemia				0.887 [a]
Yes	30 (17.3)	13 (16.9)	17 (17.7)	
No	143 (82.7)	64 (83.1)	79 (82.3)	
Ischemic heart disease				0.488 [a]
Yes	9 (5.2)	3 (3.9)	6 (6.3)	
No	164 (94.8)	74 (96.1)	90 (93.8)	
Tuberculosis infection				0.256 [a]
Yes	8 (4.6)	2 (2.6)	6 (6.3)	
No	165 (95.4)	75 (97.4)	90 (93.8)	
HIV disease				0.575 [a]
Yes	6 (3.5)	2 (2.6)	4 (4.2)	
No	167 (96.5)	75 (97.4)	92 (95.8)	
Psychiatric illness				0.613 [a]
Yes	4 (2.3)	1 (1.3)	3 (3.1)	
No	169 (97.7)	76 (98.7)	93 (96.9)	
Symptoms on presentation				
Fever				0.355 [a]
Yes	108 (62.4)	51 (66.2)	57 (59.4)	
No	65 (37.6)	26 (33.8)	39 (40.6)	
Lethargy				0.081 [a]
Yes	47 (27.2)	26 (33.8)	21 (21.9)	
No	126 (72.8)	51 (66.2)	75 (78.1)	
Headache				0.828 [a]
Yes	48 (27.7)	22 (28.6)	26 (27.1)	
No	125 (72.3)	55 (71.4)	70 (72.9)	
Altered behaviour				<0.01 [a]
Yes	90 (52.0)	54 (70.1)	36 (37.5)	
No	83 (48.0)	23 (29.9)	60 (62.5)	
Weakness				0.492 [a]
Yes	7 (4.0)	4 (5.2)	3 (3.1)	
No	166 (96.0)	73 (94.8)	93 (96.9)	
GCS on presentation, n (%)				0.021 [a]
GCS 3-9	14 (8.1)	2 (2.6)	12 (12.5)	
GCS 10-15	159 (91.9)	75 (97.4)	84 (87.5)	
CSF culture findings, n (%)				0.864 [a]
Positive growth	40 (23.1)	21 (27.3)	19 (19.8)	
No growth	118 (68.2)	49 (63.6)	69 (71.9)	
Not available	15 (8.7%)	7 (9.1)	8 (8.3)	
CSF culture growth type, n (%)				0.939 [a]
Bacterial	5 (2.9)	3 (3.9)	2 (2.1)	
Viral	20 (11.6)	9 (11.7)	11 (11.5)	
Fungal/Cryptococcal	2 (1.2)	1 (1.3)	1 (1.0)	
Parasitic/Toxoplasma	3 (1.7)	2 (2.6)	1 (1.0)	
No growth	128 (74.0)	55 (71.4)	73 (76.0)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	

Table I: Sociodemographic, clinical characteristics and investigation parameters of study participants with seizure presentation

Demographic/Clinical characteristics	Total (N=173)	No seizure (N=77)	With seizure (N=96)	p-value
CSF investigation findings, n (%)				
Low Glucose levels (<2.22 mmol/L)				0.862 [a]
Yes	18 (10.4)	9 (11.7)	9 (9.4)	
No	140 (80.9)	61 (79.2)	79 (82.3)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Elevated Protein levels (>400 mg/dL)				0.271 [a]
Yes	95 (54.9)	47 (61.0)	48 (50.0)	
No	63 (36.4)	23 (29.9)	40 (41.7)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Cell count/ Pleocytosis (WBC ≥5 cells/μ)				0.271 [a]
Present	9 (5.2)	6 (7.8)	3 (3.1)	
Absent	149 (86.1)	64 (83.1)	85 (88.3)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Neuroimaging findings, n (%)				0.425 [a]
Abnormal	86 (49.7)	34 (44.2)	52 (54.2)	
Normal	85 (49.1)	42 (54.5)	43 (44.8)	
Not available	2 (1.2)	1 (1.3)	1 (1.0)	
EEG findings, n (%)				0.003 [a]
Abnormal	109 (63.0)	38 (49.4)	71 (74.0)	
Normal	54 (31.2)	32 (41.6)	22 (22.9)	
Not available	10 (5.8)	7 (9.1)	3 (3.1)	
Type of seizure, n (%)				-
Focal seizure	26 (15.0)	0 (0.0)	26 (27.1)	
Generalized seizure	70 (40.5)	0 (0.0)	70 (72.9)	
No seizure	77 (44.5)	77 (100)	0 (0.0)	
Seizure frequency/month, n (%)				-
No seizure	77 (44.5)	0 (0.0)	0 (0.0)	
1 -2 seizure	52 (30.1)	0 (0.0)	0 (0.0)	
3 -4 seizure	31 (17.9)	0 (0.0)	0 (0.0)	
5 or more seizure	13 (7.3)	0 (0.0)	0 (0.0)	
Status Epilepticus, n (%)				-
Yes	26 (15.0)	0 (0.0)	26 (27.1)	
No	147 (85.0)	77 (100)	70 (72.9)	
Medication status, n (%)				-
No antiseizure medication	100 (57.8)	77 (100)	23 (24.0)	
Single antiseizure medication	53 (30.6)	0 (0.0)	53 (55.2)	
2 or more antiseizure medication	20 (11.6)	0 (0.0)	20 (20.8)	
		Mean ± SD (95% CI)		
Age (years)		46.80 ± 20.0 (43.8 – 49.8)		
		Median (Percentile 25th, 75th)		
GCS on presentation		14 (11, 15)		
Onset of seizure after encephalitis presentation		1 (0, 2)		
Seizure frequency within 1 month		1 (0, 3)		
Number of anti-seizure medications		0 (0,1)		

[a] Chi-square test

Statistically significant results ($p < 0.05$) are indicated in bold.

Associated factors and Independent Predictors of Seizure risk in infective encephalitis

Simple binary logistic regression was performed to determine the association between clinical and diagnostic variables and the occurrence of seizures among patients with infective encephalitis (Table III). Bivariate analysis showed that altered behaviour ($p<0.001$), low GCS on presentation ($p=0.024$), and abnormal EEG ($p=0.001$) findings were significantly associated with seizure occurrence. Other parameters, including age, gender, comorbidities, fever on presentation, low CSF glucose levels, elevated CSF protein and the presence of CSF pleocytosis, were not significantly associated with seizure occurrence.

A multivariate binary logistic regression was performed to identify independent risk factors associated with seizure occurrence in infective encephalitis (Table IV). Variables included in the model were those found to be statistically significant in the bivariate analysis and clinically relevant factors identified from prior literature of encephalitis, to ensure a robust and comprehensive model.

The overall multivariate model was statistically significant, $\chi^2(10, N=173) = 45.987$, $p < 0.001$, indicating that the set of predictors reliably distinguished between patients with and without seizures. The model explained 23.3% to 31.2% of the variance (Cox & Snell R^2, Nagelkerke R^2) and correctly classified 55.5% of cases. Goodness-of-fit was confirmed by a

Table II: Association between seizure characteristics and Glasgow Outcome Score (GOS) among patients with infective encephalitis

Glasgow Outcome scale (GOS) Score	[1] Death	[2] Neuro-vegetative state	[3] Severe disability	[4] Moderated disability	[5] Good recovery	Total	p-value
Seizure							0.165
Yes	9 (9.4)	2 (2.1)	11 (11.5)	4 (4.2)	70 (72.9)	96 (100)	
No	5 (6.5)	0 (0.0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
Type of Seizure							0.287
No seizure	5 (6.5)	0 (0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
Focal	1 (3.8)	1 (3.8)	2 (7.7)	1 (3.8)	21 (80.8)	26 (100)	
Generalized	8 (11.4)	1 (1.4)	9 (12.9)	3 (4.3)	49 (70.0)	70 (100)	
Status Epilepticus							<0.001
Yes	4 (15.4)	2 (7.7)	7 (27.0)	1 (3.8)	12 (46.2)	26 (100)	
No	10 (6.8)	0 (0)	8 (5.4)	11 (7.5)	118 (80.3)	147 (100)	
Seizure frequency/ month							0.008
No seizure	5 (6.5)	0 (0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
1 -2 seizure	5 (9.6)	0 (0)	4 (7.7)	3 (5.8)	40 (76.9)	52 (100)	
3 -4 seizure	3 (9.7)	1 (3.2)	2 (6.5)	1 (3.2)	24 (77.4)	31 (100)	
5 or more	1 (7.7)	1 (7.7)	5 (38.5)	0 (0)	6 (56.1)	13 (100)	

Significant p value <0.05

Table III: Simple logistic regression testing association factors for seizure occurrence in infective encephalitis

Variable	Crude OR (cOR)	95% CI	p-value
CSF protein			
Normal	Ref	0.295 – 1.062	0.076
High (>400 mg/L)	0.560		
EEG			
Normal	Ref	1.540 – 5.518	0.001
Abnormal	2.915		
GCS on presentation			
10–15	Ref	1.139 – 6.481	0.024
3–9	0.024		
Brain imaging			
Normal	Ref	0.818 – 2.731	0.191
Abnormal	1.495		

cOR: Crude Odds ratio
95% CI – 95% Confidence Interval
Significant p value <0.05

Table IV: Multivariate Binary logistic regression in predicting seizures in patients with infective encephalitis

Variable	B	SE	Wald	df	p	aOR	95% C.I. for OR	
							LL	UL
Age (years)								
18–44			1.844	2	0.398			
45–64	-0.665	0.500	1.766	1	0.184	0.514	0.193	1.371
>65	-0.455	0.511	0.792	1	0.374	0.635	0.233	1.728
Comorbidities								
Yes	-0.206	0.432	0.228	1	0.633	0.814	0.349	1.896
Fever	-0.025	0.382	0.004	1	0.947	0.975	0.461	2.063
Lethargy	-0.476	0.409	1.353	1	0.245	0.621	0.279	1.386
Altered behaviour	-1.524	0.373	16.731	1	<0.001	0.218	0.105	0.452
GCS on presentation								
10 -15	Ref							
3 - 9	0.670	0.522	1.650	1	0.199	1.955	0.703	5.435
Elevated CSF protein								
(>400 mg/L)	-0.828	0.395	4.393	1	0.036	0.437	0.201	0.948
Brain imaging								
Abnormal	0.172	0.382	0.202	1	0.653	1.187	0.562	2.510
EEG abnormality	1.653	0.435	14.399	1	<0.001	5.220	2.223	12.257
Constant	0.876	0.478	3.348	1	0.067	2.400	-	-

B – Regression Coefficient
S.E – Standard Error
Wald – Chi Square statistics
df – degree of freedom
p-value – Significant p value <0.05 (in bold)
aOR– Adjusted Odds Ratio
95% CI – 95% Confidence Interval for adjusted odd ratio, LL - Lower Limit, UL- Upper Limit

non-significant Hosmer–Lemeshow test, $\chi^2(8, N=173) = 6.198$, $p = 0.625$, suggesting an adequate model fit. The results are reported as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and p-values.

From the multivariate logistic regression analysis, altered behaviour, elevated CSF protein and abnormal EEG findings remained significantly associated with seizure occurrence after adjusting for potential confounders.

Abnormal EEG findings were strongly associated with an increased odds of seizures risk (adjusted OR = 5.220, 95% CI = 2.22–12.26, $p < 0.001$). this suggest that patient with abnormal EEG are approximately 5.2 times higher risk of developing seizures than those without.

In contrast, patients presenting with altered behaviour had significantly lower odds of seizures (adjusted OR = 0.218, 95% CI = 0.105–0.452, $p < 0.001$). Similarly, those with elevated CSF protein levels (>400 mg/L) showed a lower likelihood of seizure occurrence (adjusted OR = 0.437, 95% CI = 0.201–0.948, $p = 0.036$). Although reduced GCS score was associated with seizures occurrence on unadjusted univariate analysis, this association lost statistical significance after adjustment for other confounders in the multivariate model.

Other variables, including age, presence of comorbidities, lethargy, fever and abnormal brain imaging were not independently associated with seizure occurrence ($p > 0.05$ for all).

In summary, abnormal EEG findings were significantly associated with increase odds of abnormal seizure risk in infective encephalitis, while altered behaviour, low GCS on presentation and elevated CSF protein levels were more commonly observed in patients without seizures. Occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes. No significant associations were found with demographic characteristics, comorbidities, or most CSF and neuroimaging parameters.

DISCUSSION

This study provides valuable insights into the prevalence and factors associated with acute seizure development in patients diagnosed with infective encephalitis in a tertiary care setting in Malaysia.

The prevalence of seizures observed in our study was 55.4%, highlighting the substantial neurological morbidity associated with encephalitis and reaffirming the role of seizures as a common and clinically significant complication in this patient population. The seizure prevalence reported in our cohort is notably higher compared to existing broader literature, where seizure rates were reported ranging from 2% to 67%, depending on differences in study design, case definitions, and underlying etiologies.[2,10] Similarly, another study focusing specifically on confirmed infectious encephalitis reported seizure rates ranging from 33% to 40%.[1] In comparison, comparable seizure rates have been observed in studies conducted within the Asian population, including, a Japanese study that reported a prevalence of 48% among patients with viral encephalitis.[17] The slightly higher prevalence in our cohort, may be attributed to the tertiary referral nature of our study centre, where more severe and neurologically complicated cases are managed. Furthermore, the relatively high proportion of patients with status epilepticus (27.1%), along with the availability of routine EEG monitoring likely contributed to improved detection and classification of seizure activity.

In addition to determining seizure prevalence, this study systematically evaluated sociodemographic profiles and clinical characteristics to identify potential risk factors and predictive markers for seizure occurrence in patients with infective encephalitis. Neither gender nor ethnicity demonstrated a significant association with seizure development, a finding consistent with prior studies.[2,6] Although isolated reports have suggested that younger age may be a potential risk factor for seizures in encephalitis[6], this was not supported by multicentre data [2], nor was it observed in our study. Similarly, comorbidities such as hypertension and diabetes mellitus did not significantly influence seizure risk —a finding that has not been previously reported in the encephalitis literature, where systemic comorbidities remain largely underexplored. Most existing evidence come from chronic epilepsy cohorts, where these conditions are more prevalent among them.[18,19] The absence of such associations in acute infective encephalitis may reflect fundamental differences in seizure pathophysiology between acute neuroinflammatory processes and chronic epileptic syndromes.

Although lethargy and behavioural changes are frequent clinical features in encephalitis, their predictive value for seizures remains inconsistent. In our study, altered behaviour was significantly associated with reduced odds of seizures, consistent with previous reports, where behavioural disturbances were more frequently observed among non-seizure patients with encephalitis.[4] This suggests that, despite their common occurrence, these symptoms may not serve as independent predictors of seizure risk in encephalitis. A plausible explanation for this discrepancy lies in the timing of clinical assessments. As highlighted in prior research, postictal evaluations, especially in retrospective or non-seizure-focused studies—may obscure or under-represent behavioural abnormalities, leading to inconsistent associations with seizure risk.[2,20]

Reduced levels of consciousness, as assessed by the GCS have been consistently linked to an increased risk of seizures across multiple studies.[2,6,13] Although our study initially demonstrated a link between lower GCS and seizure occurrence in the unadjusted analysis, this association lost significance after adjustment for confounding factors. Collectively, these findings indicate that the relationship between reduced GCS and seizure occurrence may be mediated by other clinical or diagnostic variables, such as EEG abnormalities, suggesting that depressed consciousness reflects the extent and severity of encephalitic injury rather than a direct increase in seizure risk. There are various mechanisms which contribute to the seizure risk in patients with encephalitis, including neuroinflammation, activation

of the innate and adaptive immunity, dysregulation of microglial activity and cytokine production. The epileptogenic frontotemporal area is typically affected in Herpes simplex encephalitis, which affects the GCS state. These findings highlight the importance of distinguishing seizure-specific predictors from nonspecific encephalopathic features in the context of infective encephalitis.[21]

Among the CSF parameters, only elevated CSF protein levels were significantly associated with reduced odds of seizure occurrence, while low glucose and pleocytosis did not demonstrate a significant association with seizure risk in our study. These findings are consistent with multiple prior studies.[22–25] This likely reflects the multifactorial pathophysiology of encephalitis, which involves complex immune-mediated mechanisms such as blood–brain barrier disruption, cytokine-induced neuroinflammation, and neuronal hyperexcitability [26–28], none of which are fully captured by conventional CSF biochemical analysis.[20] For instance, elevated CSF protein may indicate neuroinflammation, but it does not necessarily reflect focal neuronal injury or excitability that could precipitate seizures. Although these CSF abnormalities remain fundamental in diagnosing encephalitis and determining its aetiology, their utility in stratifying seizure risk appears limited. Therefore, while CSF analysis remains indispensable for diagnostic purposes, it should not be relied upon as a standalone tool for predicting seizure risk in encephalitis.

Neuroimaging aids in the diagnosis of encephalitis by detecting structural abnormalities such as cerebral oedema, focal lesions and haemorrhagic changes.[29,30] Specific radiological patterns such as bilateral temporal lobe involvement and extensive cortical lesions have been linked to worse neurological outcomes and increased morbidity.[31] Despite its diagnostic value, our study did not demonstrate a statistically significant association between radiological abnormalities and seizure occurrence. This observation is supported by prior studies indicating that conventional imaging techniques may lack the sensitivity to detect transient or subtle electrophysiological disruptions associated with seizures.[2,32] Moreover, variability in imaging techniques, the timing of scans relative to seizure onset, and the presence of subclinical seizures may contribute to the absence of a detectable correlation.

EEG is a well-established diagnostic and prognostic modality in encephalitis, facilitating the detection of both clinical and subclinical seizure activity.[33] Characteristic EEG patterns, particularly lateralized periodic discharges (LPDs), have been strongly linked to higher seizure risk and worse clinical outcomes.[34-36] In our study, EEG abnormality emerged as the strongest independent predictor of seizures. Notably, 49.4% of EEG abnormalities were observed in patients without clinically apparent seizures, suggesting the presence of subclinical or non-convulsive seizure activity. The mechanisms of epileptogenesis include increased blood-brain barrier permeability, direct neuronal damage and ion channels modification, which ultimately lead to altered neuronal excitability and seizure generation. These results are consistent with previous works,[33,37–39] which emphasized the prognostic utility of EEG in predicting seizure risk and informing early therapeutic interventions.

Our study strengthens prior evidence that seizure burden, particularly status epilepticus and increase seizure frequency has a decisive impact on functional outcome, with affected patients demonstrating markedly poorer recovery at discharge. Consistent with earlier studies,[20] we found that prolonged or recurrent seizures were associated with lower GOS scores, reflecting the role of sustained cortical hyperexcitability in driving neurological decline. Although long-term outcomes were not assessed, the observation that most patients achieved seizure control with monotherapy suggests that early recognition and targeted antiseizure therapy may help mitigate secondary brain injury and support better functional recovery. Collectively, these findings highlight the importance of early EEG monitoring and prompt antiseizure management to improve functional recovery in infective encephalitis.

Overall, our study findings highlight the multifactorial nature of seizure pathophysiology in infective encephalitis. EEG abnormalities directly reflect cortical hyperexcitability and remain a robust clinical indicator of seizure susceptibility, whereas altered behaviour and elevated CSF protein levels represent broader encephalopathic processes that are not specific to seizure generation. Furthermore, seizure burden, particularly status epilepticus and high-frequency seizures has a more profound impact on neurological outcomes. These observations underscore the need for early EEG monitoring and clinical stratification based on neurological presentation to improve seizure risk prediction and enable more targeted management in patients with encephalitis. Furthermore, the observed link between early seizures and poorer outcomes further supports the need for timely recognition and intervention.

LIMITATIONS

The single-centre, retrospective design of this study limits generalisability and precludes causal inference. There is a potential for selection or information bias. Variability in EEG and CSF availability may have influenced some associations, while reliance on clinician judgement for clinical features such as altered behaviour introduces subjectivity. The absence of long-term follow-up further restricts conclusions regarding seizure recurrence and functional recovery. Future prospective, multi-centre studies with standardised protocols are needed to validate these findings.

CONCLUSION

Seizures are a common and clinically significant complication of infective encephalitis, frequently associated with increased morbidity, prolonged hospitalization, and an elevated risk of post-encephalitic epilepsy. In this cohort, seizures occurred in more than half of affected patients, underscoring their substantial clinical burden and the importance of timely recognition and management, both in the acute phase and in shaping long-term neurological outcomes.

Occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes. This study identified EEG abnormalities as the most consistent and clinically relevant predictor of seizure

occurrence. These findings emphasise the value of incorporating early EEG monitoring into standard evaluation protocols for patients with infective encephalitis. Such measures enable the timely identification of high-risk individuals, facilitate early targeted interventions, and may ultimately reduce seizure burden while limiting secondary neuronal injury.

Conversely, CSF parameters, neuroimaging abnormalities, and behavioural changes did not demonstrate a significant increased seizure risk, highlighting the limitations of relying solely on structural or biochemical markers. The heterogeneity of clinical presentations and diagnostic findings further supports the need for an integrative approach, where functional and electrophysiological assessments are prioritised over isolated diagnostic parameters.

Taken together, these results contribute to a better understanding of the early clinical trajectory of seizure development in infective encephalitis and provide a foundation for improving clinical decision-making in the acute phase. Future research should prioritise prospective, multicentre validation across diverse populations and explore the integration of immunological and molecular biomarkers to refine prognostication and guide the development of precision-based seizure risk stratification models in encephalitis.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

INFORMED CONSENT STATEMENT

Patient consent was waived due to it being a retrospective study spanning across 9 years and de-identification before data analysis.

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ORIGINAL ARTICLE

Measles in Selangor: A Comparative Analysis Between Adults and Children Using the E-Measles Registry, 2015-2024

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ABSTRACT

Introduction: Measles remains a persistent public health concern in Malaysia. Despite sustained high vaccination coverage in states such as Selangor, reported cases continue to increase. This trend suggests a possible shifting age-distribution of measles, a pattern that has been observed in countries with a high vaccination rate. Understanding the epidemiology and clinical characteristics of measles between adults and children is critical in guiding targeted public health interventions aimed at control and elimination of measles. This study aimed to describe the incidence of measles in adults and children in Selangor, and to compare their sociodemographic, clinical, vaccine, and exposure-related differences.

Materials and Methods: This comparative cross-sectional study used secondary data from the Selangor e-Measles Registry from 2015 to 2024. Confirmed cases were classified as adults (≥18 years) and children (<18 years). The incidence of each group was calculated annually over ten years. Descriptive statistics, chi-square test, Fisher's exact test, and Mann-Whitney U test were used to describe and compare the differences between the two groups. Data were analysed using SPSS version 29.

Results: A total of 3954 confirmed measles cases were included in the study, with 540 (13.7%) adult cases and 3414 (86.3%) cases in children. Between 2015 and 2024, the incidence of measles was consistently higher in children as compared to adults, with risk ratios ranging from 14.43 (95% CI: 11.25, 18.73) in 2017 to 87.65 (95% CI: 27.39, 278.66) in 2022. With the exception of 2019-2022, adults showed a gradual increase in number over the study period, with the highest proportion in 2023 (16.4%). Significant differences between adults and children were observed (p<0.05) according to nationality, ethnicity, clinical symptoms, hospitalisation, complications, vaccination status, and duration since the last vaccination.

Discussion: The findings suggest that despite the increase in adult cases, measles predominantly affects children in Selangor. The findings highlight the need to strengthen vaccination efforts through the National Immunisation Programme (NIP) and prioritising Supplementary Immunisation Activities (SIAs) among children aged below 6 years old. Additionally, the gradual rise in cases in adults and children aged 7-12 years old should be monitored closely to detect emerging epidemiological shifts. Significant clinical differences between adults and children highlight the need for training of healthcare providers and public education to support diagnosis, prevent outbreaks, and avoid complications. Digitalisation of health records, such as the documentation of vaccination history, is needed. Conclusion: Measles in Selangor showed age-specific trends and differences. Addressing these issues through strengthened childhood immunisation, targeted interventions and continuous surveillance is essential to achieve measles control and elimination in Selangor and Malaysia.

KEYWORDS:
Measles, Adult, Children, Comparative analysis, Registry

INTRODUCTION

Measles is a highly contagious viral disease with an estimated basic reproductive number (R_0) of 9-18, one of the highest for direct transmission. R_0 reflects the average number of secondary cases that can occur on the introduction of an infectious person to a susceptible population.[1] Prior to the introduction of the measles vaccine in 1963, an estimated 2.6 million measles deaths occurred each year globally.[2] With the increased coverage of vaccination worldwide, a 73% decrease in measles deaths was observed between 2000 and 2018.[3] The availability of a safe and effective vaccine, absence of animal reservoirs, and readily diagnosable clinical symptoms make it a suitable disease for global eradication, with all World Health Organization (WHO) regions committing to measles elimination.[4]

In the Western Pacific Region (WPR), Singapore, Brunei, Australia, Japan, Korea, New Zealand, Macao, and Hong Kong have achieved Measles Elimination as early as 2014. Despite the global measles resurgence in 2018-2019, they managed to maintain a measles incidence of <1 per million population from 2021 to 2023, which is the target for elimination.[5] This contrasts with Malaysia, which, although committed to measles elimination since 2004 and maintains high immunisation coverage, reported an increase in the trend of confirmed measles from 3.8 to 58.7 per million population between 2021 and 2023, the highest in the WPR

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in 2023.[6] Selangor, the most populous state in Malaysia, undoubtedly contributed to this burden, reporting 70.9 cases per million population in 2023 despite maintaining vaccination coverage above 95%.[7]

This paradox between the high coverage but rising incidence raises concerns about a shifting epidemiology to involve more adults. This has been observed in countries like China, where adults aged 26 to 45 years became one of the primary sources of measles after the implementation of their nationwide SIAs.[8] In Spain, 68.9% of cases were aged >20 years.[9] This shift has raised important questions about the clinical presentation, severity, and outcomes of measles among adults and whether they differ from those in children. Several studies have demonstrated that adults are more likely to be hospitalised and develop complications. For instance, a study in France reported higher hospitalisation rates and increased diarrhoea with dehydration compared to children.[10] However, most of these studies were hospital-based and focused on clinical outcomes, often neglecting broader sociodemographic, vaccine, and exposure-related variables of interest.

In Malaysia, research and interventions have mostly targeted children. A recent study suggest that older age is associated with higher odds of contracting measles.[11] This is concerning because measles is commonly perceived as a disease affecting children. Clinicians may not suspect it in adult patients who initially present with fever and cough. A delay in diagnosis leads to late isolation, inappropriate treatment, and an increased risk of complications.[12] Adults may also unknowingly serve as index cases during outbreaks, as reported in an outbreak in Sweden.[13]

Although global reports have highlighted a shift in measles epidemiology toward adults in countries with high vaccination coverage, such a trend has not been formally documented in Malaysia. Given the lack of local data comparing adult and child measles cases at the population level, this study's primary objective was to describe the age-specific trend of measles' incidence in Selangor from 2015-2024, using secondary data from Selangor's e-Measles Registry. The second objective was to describe and determine whether significant sociodemographic, clinical, exposure, and vaccine-related differences existed between adults and children with measles in Selangor.

MATERIALS AND METHODS

Study Design

This comparative cross-sectional study was designed to compare sociodemographic, clinical-related, exposure-related, and vaccine-related aspects of measles in adults and children in Selangor from to 2015-2024 using secondary data from the e-Measles Registry.

Study Area

This study was conducted in Selangor, Malaysia. Selangor has a total population of 7.4 million in 2024, the highest in Malaysia.14 For the purpose of monitoring diseases and health programmes, the Selangor State Health Department has divided the districts into large districts (Petaling, Hulu Langat, Klang and Gombak) and small districts (Sepang, Hulu Selangor, Kuala Langat, Kuala Selangor and Sabak Bernam) based on the total population, with large districts having a population of >900,000 people.[14]

Study Population, Sample and Data Source

This study included two study populations. The first population comprised all confirmed cases of adults (aged ≥18 years) with measles in Selangor, and the second population comprised all confirmed cases of children (aged <18 years) with measles in Selangor. Samples for each population were obtained from the Selangor e-Measles Registry from 2015 to 2024. A confirmed case is defined as any "laboratory-confirmed case detected by the presence of measles-specific IgM antibodies or measles virus in clinical samples",[15] or that is "clinically compatible with measles with an epidemiological link to a confirmed case",[15] or "clinically compatible without an epidemiological link or lab confirmation but was decided to be registered by the Expert Review Committee".[16] All confirmed measles cases from the e-Measles Registry Selangor from 2015-2024 of all nationalities were included in the sample. The sample excluded imported cases of measles.

The Selangor e-Measles Registry is an online database system used by the Ministry of Health Malaysia since 2005 to standardise and record the investigation and registration of measles cases in Malaysia. The data in the e-Measles Registry comprises all suspected measles cases that have been registered in the e-Notification system. These cases were investigated within 48 hours, and once confirmed to be measles, the cases will be registered either as laboratory-confirmed measles, epidemiologically-linked measles, or clinically compatible measles. The data owner is the Communicable Disease Control (CDC) Unit, Selangor State Health Department, at the state level.

For the calculation of incidence, data for the denominator, which is the total population of children (aged below 18 years) and adults (aged ≥18 years) in Selangor, were obtained upon request by email from the Department of Statistics Malaysia, through their official website. The data was shared in Microsoft Excel format by the Chief Assistant Director of the Population and Demography Division.

Sample Size Calculation

Minimum sample size was calculated using Pocock's formula for two proportions with the level of significance set at 0.05 and the power of the study set at 80%. Considering 20% missing data, using proportions reported by Zhao et al.,[17] the calculated minimum sample size for each group was 279 cases. However, for this research, universal sampling was done for all eligible and clean confirmed adults and children measles cases obtained from e-Measles Registry Selangor from 2015-2024.

Study Variables

Variables included and sourced from e-Measles Registry were sociodemographic variables (gender, ethnicity, nationality and residential district), clinical related variables (fever, cough, coryza, conjunctivitis, hospitalisation, developed complications, diarrhoea, pneumonia and other

complications), exposure related variables (contact history, case status and case detection) and vaccine-related variables (vaccination status, type of healthcare facility providing the dose, time since last vaccination).

Data Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 29.0 IBM SPSS Inc.

In accordance with the first objective, which was to describe the age-specific trend of measles' incidence in Selangor from 2015-2024, the following formula was used to calculate the annual incidence of measles in adults and children:

$$\frac{\text{Number of age-specified measles cases in a specified year}}{\text{Mid-year age-specified population estimates in a specified year}} \times 1{,}000{,}000$$

Subsequently, Poisson regression with log link and population offset was used to assess annual changes in measles incidence separately for adults and children. Year was entered as a categorical variable, and statistical significance for year-to-year differences was evaluated using Wald p-values.

As for the second objective, the sociodemographic, clinical, vaccine, and exposure-related factors of adult and child measles in Selangor from the e-Measles registry from 2015-2024 were described according to the types of variables. Continuous variables are described as median and interquartile range (IQR). Categorical variables are described in frequency and proportion, n (%). Following that, the Chi-square test and Fisher's exact test were used to compare categorical data, and the Mann–Whitney U test was used to compare continuous data to determine the differences between adults and children with measles in Selangor.

Data Collection, Extraction and Management

Data without identifiers were obtained from the data owners at the CDC Unit, Selangor State Health Department. The downloaded data from the e-Measles Registry were in Microsoft Excel format. Missing data were analysed and cleaned. Using a reputable source that is transparent in its data collection method and regularly monitored by the data owner helped reduce potential measurement bias and enhance data validity. Our analysis found that only 20 of 3981 cases had missing data. Listwise deletion was used for missing data. The final sample was transferred to the Statistical Package for the Social Sciences (SPSS) software version 29.0, IBM SPSS Inc., for further analysis. Figure 1 shows how the data was managed after data collection.

To ensure privacy and confidentiality, all personally identifiable information, such as name, identification number, address, and phone number, was omitted by data owners prior to the data being handed over for further management. For ease of identification during data management and analysis, an "ID" column was created using numbers starting from 1 to n (reflecting the total number of cases) based on the order of data received. The data received were safely stored in a password-protected folder and computer, accessible only to members of the research team.

RESULTS

Table I shows the annual incidence of measles in adults and children in Selangor from 2015-2024. The lowest incidence in children was 12 per million population in 2021, and the highest incidence was 396.6 per million population in 2018. The lowest incidence in adults was 0.2 per million population in 2021, and the highest incidence was 27.1 per million population in 2018. The relative risk (RR) of contracting measles was 14.4-87.7 times higher in children than in adults.

Figure 2 shows the trend of cases and incidence of measles according to age group. The incidence of measles in children showed an increasing trend from 2015 to 2018, before dropping in 2019 to 2022 and subsequently rose back in 2023 and 2024. The number of measles cases in children ranged from 22 to 728. A similar trend is seen in adults, but to a lesser degree. Cases of measles in adults ranged from 1 to 135 cases. The drop in 2019-2022 was related to the pandemic effect of COVID-19. Poisson regression confirmed the trend to be statistically significant. Adults and children both showed significant increases in 2018 ($p<0.001$) and significant decreases from 2019-2022, with the strongest reductions in 2020-2021 (all $p<0.001$).

Table II shows the annual number of measles cases and incidence in Selangor. Children were categories into four age groups: <1 year old, 1-6 years old, 7-12 years old and 13-17 years old. The highest yearly incidence was among children aged <1 year. Further analysis of our data suggests that out of all the confirmed cases in children <1 year old, 950(66.8%) were not yet eligible for vaccination. This equals 88.3% of the unvaccinated in the <1 year age group.

Table III shows the sociodemographic, clinical, vaccine, and exposure-related characteristics of measles in adults and children. It also compares the differences in characteristics between adults and children. There were 3954 cases included in this research- 3414 (86.3%) were children and 540 (13.7%) were adults. The majority of both adults and children, who were Malays, detected through passive case detection, were sporadic cases and did not require hospitalisation. Most children had incomplete vaccination, whereas most adults' vaccination status were unknown. There were several significant differences ($p<0.05$) between measles cases among adults and children in Selangor, namely nationality, ethnicity, clinical symptoms (coryza and conjunctivitis), hospitalisation, developing complications such as diarrhoea and other complications, vaccination status, and duration from the last vaccination.

DISCUSSION

Trend

Children are at a higher risk of contracting measles. Further age-specific division among children revealed that the incidence in children was highest in the age group of <1 year. The high burden of cases among children not yet eligible for vaccination prompted the change in the vaccination protocol in the NIP in 2016, where the first dose was administered at nine months of age and a booster was administered at 12 months of age. This subsequently led to a decrease in the

Table I: Incidence of confirmed measles cases among adults and children in Selangor from 2015-2024 (N=3954)

Age group (years)	Number of confirmed case (N)	Total population at risk	Cumulative incidence (per 1,000,000 population)	Incidence (per 1,000,000 population) by age group	RR (95%CI)	Incidence in Children / Incidence in Adults
2015						
<18 years old	487	1,785,400	85.5	272.8		21.58
≥18 years old	58	4,588,700		12.6		(16.44, 28.22)
2016						
<18 years old	585	1,804,400	103.4	324.2		17.01
≥18 years old	90	4,723,300		19.1		(13.60, 21.12)
2017						
<18 years old	384	1,818,900	68.2	211.1		14.43
≥18 years old	71	4,852,900		14.6		(11.25, 18.73)
2018						
<18 years old	728	1,835,600	126.7	396.6		14.62
≥18 years old	135	4,977,700		27.1		(12.18, 17.46)
2019						
<18 years old	179	1,850,100	29.6	96.8		19.50
≥18 years old	25	5,039,500		5.0		(12.94, 29.37)
2020						
<18 years old	86	1,864,800	12.9	46.1		59.14
≥18 years old	4	5,129,600		0.8		(21.76, 160.77)
2021						
<18 years old	22	1,837,400	3.3	12.0		61.99
≥18 years old	1	5,177,300		0.2		(8.41, 459.44)
2022						
<18 years old	91	1,812,600	13.3	50.2		87.65
≥18 years old	3	5,237,700		0.6		(27.39, 278.66)
2023						
<18 years old	427	1,817,500	70.9	234.9		15.08
≥18 years old	84	5,392,200		15.6		(11.82, 19.11)
2024						
<18 years old	425	1,825,800	67.1	232.8		18.68
≥18 years old	69	5,537,600		12.5		(14.59, 24.05)

Table II: Number of cases and age-specific incidence of confirmed measles cases among children in Selangor from 2015-2024 (N=3414) *

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
<1 year old	165 (1601.9)	234 (2310.0)	186 (1888.3)	362 (3641.9)	113 (1198.3)	64 (709.5)	16 (175.6)	51 (598.6)	119 (1309.1)	113 (1314.0)
1-6 years old	247 (416.8)	271 (445.6)	142 (226.9)	264 (411.1)	50 (75.8)	18 (26.9)	5 (7.7)	33 (51.9)	187 (293.7)	149 (231.0)
7-12 years old	58 (99.4)	54 (93.0)	39 (67.8)	59 (103.3)	16 (27.6)	4 (6.7)	1 (1.7)	6 (9.9)	95 (154.5)	135 (218.3)
13-17 years old	17 (33.6)	26 (50.6)	17 (32.7)	43 (82.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	26 (54.8)	28 (58.80)

*Number of cases (Age-specific incidence per million population)

number of cases among that population, although it is still the major cause of unvaccinated measles cases among children <1 year old. It is worth noting, primary vaccine failure is seen higher in children immunised <1 year old due to underdeveloped immunity and interference by maternal antibodies.[18] Another study among Dutch children revealed that despite having received two doses of MMR, >70% of children who had their first vaccination before 8.5 months lost their protective antibody levels within six years, suggesting that vaccinating too early might also result in secondary vaccination failure.[19] Hence, any decision on hastening the timing of vaccination should be balanced between the risks of measles occurring before vaccination and the risks of vaccination failure, which decreases with increasing age.[20] The next age group with the highest incidence suitable for targeted interventions, such as SIA, are in the 1-6 years category. Despite the reported high vaccination coverage in Selangor, the resurgence of cases suggests an immunity gap that might have happened during COVID-19 pandemic. This was highlighted by the WHO stating that COVID-19 led to the interruption of vaccination, with over 178 million people worldwide at risk of missing vaccines in 2020.[21] The MCV1 coverage reportedly declined from 86% in 2019 to 81% in 2021.[22]

Although our study reported the highest proportion and incidence of cases to be below 6 years old, with Cambodia, Thailand, and Indonesia having a similar burden, we differed from other countries such as the United States, which reported the highest transmissibility occurred among school

Table III: Comparison between adults and children with measles in Selangor from year 2015 to 2024 (N =3954)

	Variables		Adult =>18 years old n=540	Children <18 years old n=3414	p-value
	Sociodemographic Variables				
1	Gender	Male	272 (50.4%)	1834 (53.7%)	0.147[c]
		Female	268 (49.6%)	1580 (46.3%)	
2	Nationality	Malaysian	491 (90.9%)	3235 (94.8%)	<0.001[c]
		Non-Malaysian	49 (9.1%)	179 (5.2%)	
3	Ethnicity	Malay	429 (79.4%)	2985 (87.4%)	<0.001[c]
		Chinese	29 (5.4%)	127 (3.7%)	
		Indian	23 (4.3%)	70 (2.1%)	
		Others	59 (10.9%)	232 (6.8%)	
4	District	Small Districts	90 (16.7%)	475 (13.9%)	0.089[c]
		Large Districts	450 (83.3%)	2939 (86.1%)	
	Clinical variables				
1	Fever	No	5 (0.9%)	15 (0.4%)	0.179[f]
		Yes	535 (99.1)	3399 (99.6%)	
2	Cough	No	120 (22.2%)	764 (22.4%)	0.935[c]
		Yes	420 (77.8%)	2650 (77.6%)	
3	Coryza	No	254 (47.0%)	1244 (36.4%)	<0.001[c]
		Yes	286 (53.0%)	2170 (63.6%)	
4	Conjunctivitis	No	359 (66.5%)	2495 (73.1%)	0.001[c]
		Yes	181 (33.5%)	919 (26.9%)	
5	Hospitalisation	No	353 (65.4%)	2511 (73.6%)	<0.001[c]
		Yes	187 (34.6%)	903 (26.4%)	
6	Developed Complications	No	422 (78.1%)	2990 (87.6%)	<0.001[c]
		Yes	118 (21.9%)	424 (12.4%)	
7	Diarrhoea	No	473 (87.6%)	3209 (94.0%)	<0.001[c]
		Yes	67 (12.4%)	205 (6.0%)	
8	Pneumonia	No	535 (99.1%)	3379 (99.0%)	0.83[c]
		Yes	5 (0.9%)	35 (1.0%)	
9	Other Complications	No	470 (87.0%)	3194 (93.6%)	<0.001[c]
		Yes	70 (13.0%)	220 (6.4%)	
	Vaccination variables				
1	Vaccination Status	No	202 (37.4%)	1996 (58.5%)	<0.001[c]
		Complete	43 (8.0%)	413 (12.1%)	
		Incomplete	49 (9.1%)	809 (23.7%)	
		Unknown	246 (45.6%)	196 (5.7%)	
2	Facility Providing Last Vaccine	Government Clinic	77 (77.0%)	961 (74.1%)	0.627[c]
		Rural Clinic	4 (4.0%)	82 (6.3%)	
		Others	19 (19.0%)	254 (19.6%)	
3	Duration from last vaccination		22.87 ± 6.49 (y) (median + IQR)	0.25 ± 2.81 (y) (median + IQR)	<0.001[m]
	Exposure variables				
1	Contact History	No	491 (90.9%)	3113 (91.2%)	0.845[c]
		Yes	49 (9.1%)	301 (8.8%)	
2	Case Detection				
	Active	23 (4.3%)	141 (4.1%)	0.889[c]	
		Passive	517 (95.7%)	3273 (95.9%)	
3	Case Status				
	Sporadic	484 (89.6%)	2984 (87.4%)	0.143[c]	
		Outbreak	56 (10.4%)	430 (12.6%)	

Abbreviations: IQR = interquartile range, y = years
[c]Chi-square Test, [f]Fisher's Exact Test, [m]Mann-Whitney U Test

children aged 5-17 years old.[23] One possible explanation is that immunisation history is mandatory to be declared at government school entry in Malaysia, where children with missed vaccines could be identified and given catch up vaccination by the school health team. Whereas in the United States, pockets of vaccine refusal exist and tend to cluster within and across schools, causing outbreaks.[24]

Despite adults having a lower risk of contracting measles, the absolute number and proportion of adults contracting measles is still of concern, with the proportion of adults (with the exception of the pandemic era) ranging from 10.64% in 2015 to 16.44% in 2023. This gradual epidemiological shift may be caused by waning immunity among people who lived in the era of single-dose vaccines and low cases, making them more susceptible to the disease.[25] Although the shift is not as prominent as in certain countries like Germany which saw a drastic increase in adults to comprise 43% of total measles cases,[26] it still warrants attention and further monitoring. Selective booster programmes could be done for this age group to curb further rise. Mat Daud et. al., in their recent study also suggested to include booster doses for older age groups or high-risk groups.[11]

Sociodemographic, clinical, and vaccine-related factors

The proportion of measles among non-Malaysian adults was higher than Malaysians. This is logical, as most non-Malaysians who come for work or studies are adults. Mat Daud et. al. stated that non-Malaysian has a higher risk of developing measles due to barriers in accessing healthcare, language, financial issues and lack of awareness regarding importance of vaccine.[11] This finding was echoed in Europe where measles outbreaks were seen highest among non-citizens which involved asylum seekers, workers and students.[27] Malays, the majority, showed a higher proportion of children with measles than other races. Vaccine hesitancy, religious issues, and low confidence in vaccines can be reasons for this situation.[28]

Coryza is more commonly seen in children, showing a significant difference compared to adults. This could be due to the anatomical structure, immature immune system, and high prevalence of atopy in children.[29] There was a significant difference between the presence of conjunctivitis in adults and children, with adults having a higher proportion of conjunctivitis than children. This finding contrasts with the findings in Beijing, where adults and children showed a similar proportion of conjunctivitis.[17] Keratoconjunctivitis in adult measles can manifest as punctuate eruption in the cornea with moderate dry eye symptoms causing severe discomfort, photophobia and foreign body sensation in the eyes.[30] A study in France noted that children were significantly less hospitalised.[10] The same study also noted that diarrhoea and dehydration were more common in adults, requiring more frequent fluid therapy. These findings align with our study, where there was a statistically significant increase in hospitalisation and complications, specifically diarrhoea, in adults compared to children. The reason behind the higher rate of complications and hospitalisations in adults could be due to underreporting or underdiagnosing of measles among adults due to a low index of suspicion. This late diagnosis can result in complications among adults with measles.[12]

In Beijing, more than 600 pneumonia cases were documented in the span of 12 years, with children having significantly higher proportions of pneumonia than adults. However, our study showed no significant differences between the proportion of pneumonia in measles cases among adults and children. The overall low number of pneumonia cases (just 40 over 10 years) suggests that the complication rate may have been underestimated in this study. This discrepancy could be due to the fact that the Beijing study was hospital-based and data were obtained from medical records throughout their hospital visits. In contrast, the Selangor data are population-based. The investigation conducted through phone calls to patients within 48 hours of notification only gives a single snapshot of the patient. The patient may not have developed pneumonia yet or may not have known that he was being treated for a mild form of pneumonia.

There was also a significant difference in the vaccination status of adults and children, with a glaringly high proportion of "unknown vaccination" in adults as compared to children (45.6% vs. 5.7%) The high unknown vaccination rates in adults are not specific to Selangor. A study in Mongolia reported that 88% of adult measles cases were uncertain about their vaccination history.[31] This makes it difficult to study their association between vaccination and disease or outbreaks. Hence, it is important to make vaccine documentation readily available. One option is to integrate it into health information systems. We can learn from the example of Louisiana. When residents of Louisiana were evacuated to Texas during Hurricane Katrina, doctors were able to retrieve their vaccination histories because the immunisation systems were online and digitally-linked.[32]

Despite this, our findings suggests that both adults and children mostly received their vaccination in government clinics (77% in adults and 74.1% in children), showing the governmental burden in relation to vaccine provision while reflecting a good documentation process in governmental health clinics that enables patients to recall their vaccination history. Proper documentation of vaccination is also important in the event of suspected vaccine storage or potency issues. The proportion of measles vaccination received in private healthcare facilities on the other hand were 1% in adults and 13.4% in children, indicating the potential role of private healthcare facilities in supporting measles vaccination delivery in the future, provided that proper documentation practices are followed.

For adults, the median duration since the last vaccination was 22.89±6.49 years. Limited research has been published on this to make comparisons within the WPR. Another study reporting on this was from Spain which reported a median of 18.8 years from date of last vaccination for cases with two vaccines and a median of 18.2 years for cases of single dose vaccine, which were attributed to waning immunity.[9]

RECOMMENDATIONS

This study recommends and supports the prioritisation of SIAs targeting children below six years old due to high age-specific incidence among this age group. We also noted a gradual increase in measles in children 7-12 years in the past two years and suggest that school health services monitor this condition closely. Although the risk of contracting measles is higher in children, threats related to adult measles in the form of complications and hospitalisations warrants continuous surveillance and mandates health practitioners to have a higher index of suspicion for adult measles cases. Health education should extend to the public, and the appearance of a diffuse rash a few days after the onset of fever should alert the public and health practitioners of the possible diagnosis of measles despite mild symptoms. Technology and health information systems should be leveraged to improve health record-keeping with regard to vaccination history extending into adulthood.

Strength and Limitations of the Study

This study reported age-specific trends and differences in measles in adults and children in Malaysia, which, to our knowledge, have not been highlighted before. The inclusion of a large dataset spanning several years helped enrich the findings by minimising selection bias. The use of data from a nationally used database decreases information bias. This analysis could help lawmakers and health authorities in policymaking and targeted interventions through immunisation or health promotion. We acknowledge that

the definition of children in this study was based on local definition and research which may limit comparability with other studies.[33] In depth comparison between age groups was not part of the scope of the study. Other limitations include limited control over the quality and accuracy of secondary data, which were mostly collected for surveillance purposes rather than for research. Registry information bias and recall bias, for example as seen in the high 'unknown' vaccination status among adults may distort associations and limits comparisons. Also, the variables compared were limited to those available in the system, limiting the comparison to other variables such as workplace/parental occupation and median household income. Finally, although the sample size was large, this study was conducted in Selangor, which might differ demographically from other areas and might not be generalisable to all settings.

Future Research

Future research should address further on refining age stratifications or focus on a certain age group to improve comparability. Longitudinal and case-control studies are better at assessing causality and associations between factors and outcomes. Studies on assessing the 'unknown' vaccination status and targeted seroprevalence studies may identify immunity gaps. It is also suggested that future research on measles complications to be based on electronic health records, which might be more sensitive in detecting late complications.

CONCLUSION

In Selangor, children experienced substantially higher measles incidence than adults throughout 2015-2024, with the greatest burden in those aged under six. Adults, however, showed more complications, hospitalisation and markedly poorer vaccination documentation. Statistically significant differences were also seen in nationality, ethnicity and clinical symptoms. These findings demonstrate clear epidemiological differences between adults and children and emphasises the need for strengthened childhood immunisation through the NIP and targeted SIAs, improved adult vaccination documentation, and closer monitoring of rising adult cases to support measles elimination in Malaysia.

Ethical Consideration

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and received ethical clearance from the UiTM Research Ethics Committee (FERC-EX-25-14) and Malaysia Medical Research Ethics Committee- NMRR ID-25-00647-YK1. Permission from the Director of the Selangor State Health Department was obtained to use secondary data from the e-Measles Registry Selangor.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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AUTHOR'S CONTRIBUTION

Conceptualisation: NSI, LSS, MM; Methodology NSI, LSS, MM; Field technical support FK, SMWM; Writing-Original Draft NSI; Writing- review and editing: all authors. All authors approved of final manuscript.

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ORIGINAL ARTICLE

Outcome of Hepatitis C Screen-and-Treat Program at a Drug Rehabilitation Centre in Perlis State

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is prevalent among people who inject drugs globally and in Malaysia. Drug rehabilitation centres (PUSPEN) offer opportunities for intervention, but the feasibility of HCV care cascades in these settings requires evaluation. This study aims to evaluate the outcome of an integrated HCV screen-and-treat program implemented at PUSPEN Perlis, Malaysia.

Materials and Methods: This retrospective cohort study analysed data from an HCV screen-and-treat program conducted between October 2022 and December 2023 at PUSPEN Perlis. The program involved initial screening with rapid antibody testing, confirmatory HCV RNA testing, APRI-based fibrosis assessment, and Direct-Acting Antiviral (DAA) treatment, with Sustained Virologic Response at 12 weeks post-treatment (SVR12) as the primary outcome.

Results: Screening of 461 participants during study period identified 62 (13.4%) as HCV antibody positive. Significant attrition occurred before confirmatory testing, with 34 (54.8%) undergoing HCV RNA tests, of whom 33 (97.0%) were positive. Treatment initiation was also limited, with 17 (51.5%) starting DAA therapy, primarily due to anticipated short rehabilitation stays. One participant transferred during therapy; the remaining 16 completed the 12-week regimen, all achieving SVR12 (100%) without reported adverse effects.

Conclusion: HCV screen-and-treat programs are feasible in Malaysian drug rehabilitation centres but face challenges in linkage to confirmatory testing and treatment initiation, largely due to limitations imposed by the duration of stay. While DAA therapy is highly effective when completed, strategies addressing diagnostic streamlining, potentially shorter regimens, and continuity of care post-release are crucial to optimise HCV elimination efforts in this vulnerable population.

KEYWORDS:
hepatitis C, drug rehabilitation centre, injecting drugs, direct-acting antivirals, Malaysia

INTRODUCTION

Drug addiction stands as a widespread and concerning global health issue, impacting millions of individuals across the world. The World Health Organization (WHO) estimates that a substantial proportion of the global population grapples with substance abuse.[1] The ramifications of drug addiction extend beyond the individual, encompassing detrimental effects on physical and mental health, interpersonal relationships, and overall economic productivity. Furthermore, drug-related criminal activities, violence, and broader social problems are frequently intertwined with substance abuse.[2] Notably, the practice of injecting drugs presents a significant avenue for the transmission of the hepatitis C virus (HCV).[3,4]

As a blood-borne pathogen, HCV is readily transmitted through the sharing of needles and other contaminated injecting tool among individuals who use drugs. The prevalence of HCV infection among people who inject drugs (PWID) is alarmingly elevated on a global scale, including within the Asian region. In Malaysia, approximately 2.5% of the adult population is estimated to be living with HCV, with injection drug use accounting for a significant 59% of these infections.[5] Several local studies reported an alarmingly high prevalence of HCV among people who inject drugs, ranging from 40.5% to a staggering 89.9%.[6,7] This underscores the critical and immediate need for effective interventions aimed at both preventing and treating HCV infection within this particularly vulnerable demographic.

Malaysia has a long-standing and recognised commitment to addressing the challenges of drug addiction and its associated issues.[8] The National Anti-Drug Agency (NADA), a key governmental body operating under the purview of the Ministry of Home Affairs, plays a central role in the management and rehabilitation of individuals struggling with drug dependence. NADA oversees a network of 30 drug rehabilitation centres, known as PUSPEN, strategically located throughout the nation.[9] One such centre is situated in Bukit Chabang, within the state of Perlis.

Individuals undergoing rehabilitation at PUSPEN participate in a comprehensive and structured program that spans to a maximum period of 24 months. This prolonged engagement

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offers a valuable window of opportunity for medical teams to systematically screen and provide treatment to individuals who may be living with HCV infection. While HCV elimination programs have demonstrated considerable success and effectiveness in the general population,[10,11] there remains a relative lack of understanding regarding their feasibility and outcomes when implemented specifically within vulnerable populations residing in drug rehabilitation centres.

In order to bridge this critical knowledge gap, a collaborative initiative was established between the Ministry of Health and the Ministry of Home Affairs. This inter-ministerial partnership facilitated the implementation of a novel screen-and-treat program at PUSPEN Perlis, with crucial support provided by a nearby health clinic. The primary aim of this study was to evaluate the outcome of this newly implemented program in enhancing the continuum of HCV care within the unique setting of a drug rehabilitation centre.

MATERIALS AND METHODS

Ethics approval

This study received approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-24-03922-JR4), in accordance with the ethical standards of the 1964 Helsinki Declaration. The requirement for informed consent was waived because the study used secondary data retrieved from the program database.

Study Design and Setting

This study employed a retrospective cohort design to evaluate the outcomes of an integrated HCV screen-and-treat program implemented at a drug rehabilitation centre (PUSPEN) in Perlis State, Malaysia. The program was conducted between October 2022 and December 2023. Data for this analysis were derived from secondary records of individuals who participated in the program, under the auspices of the Perlis State Health Department.

PUSPEN Perlis was established in 1987 with a maximum capacity of 150 clients/trainees. The main aim of its establishment is to provide treatment and rehabilitation to individuals recovering from drug addiction so they can return to their families and society, functioning as productive and accepted individuals. At the time the HCV screen-and-treat program was being implemented, the health of trainees at PUSPEN Perlis was managed by two resident Medical Assistants (MA). Trainees who require further medical attention are referred to either the Klinik Kesihatan Padang Besar (KKPB), a primary healthcare clinic, or to the Hospital Tengku Fauziah (HTF), a state tertiary hospital.

The Hepatitis C Screen-and-Treat Program Protocol

The HCV screen-and-treat program at PUSPEN Perlis was a collaborative effort involving the Perlis State Health Department, KKPB, Hospital Sultanah Bahiyah (HSB), Hospital Tuanku Fauziah (HTF), and PUSPEN Perlis. The HCV care cascade in the program was adapted from the Clinical Practice Guideline for Management of Chronic Hepatitis C in Malaysia.[12] The program incorporated the following key steps: To manage logistical constraints with a small medical team and ensure safety precautions were met, HCV screening was conducted over two separate sessions for program participants at PUSPEN Perlis. All eligible participants were gathered in the multipurpose hall in PUSPEN Perlis and briefed on the program. Subsequently, a medical team consisting of healthcare staff from PUSPEN Perlis and KKPB collected demographic data and relevant medical histories. Participants underwent an initial anti-HCV screening using a Rapid Diagnostic Test (RDT) performed on a finger prick. Those with a reactive anti-HCV result then proceeded to HCV confirmatory testing and pre-treatment assessment, which involved a venous blood draw for HCV RNA viral load, complete blood count, and liver function tests, all performed on the same day. These blood samples were subsequently sent to a designated hospital (HSB) laboratory for HCV RNA analysis. Other blood tests were managed by HTF laboratory.

Liver fibrosis status was assessed using the Aspartate aminotransferase to Platelet Ratio Index (APRI) score to determine the likelihood of cirrhosis.[13] Participants with APRI score ≥1.5 were considered to have high possibility of having liver cirrhosis. This non-invasive biomarker approach using APRI was selected as a practical and accessible method for determining the likelihood of cirrhosis in this resource-limited setting, helping to streamline Direct-Acting Antiviral (DAA) treatment initiation. Treatment with DAA medications was initiated for participants with detectable HCV RNA and either with non-cirrhotic liver or compensated cirrhosis. The medical officer and Family Medicine Specialist from KKPB performed a clinical assessment to check for any signs of liver decompensation before initiating DAA treatment. The duration of DAA therapy was determined based on the presence or absence of cirrhosis, typically 12 weeks for those without cirrhosis and 24 weeks for participants with compensated cirrhosis. Treatment initiation occurred within the PUSPEN facility. Participants identified with HCV co-infections (HIV/HCV or HBV/HCV) or those with decompensated cirrhosis were referred to the Gastroenterology team at HTF for specialised management.

Treatment completion was verified through self-reporting and medication refill records. Twelve weeks following the completion of antiviral therapy, participants were scheduled to provide blood samples for Sustained Virologic Response at 12 weeks post-treatment (SVR12) testing. Participants who did not achieve SVR12 were referred to gastroenterology clinic in HTF for further evaluation and management strategies. All data pertaining to participants enrolled in this program were systematically entered into a dedicated database maintained by the HIV/STD/HEPC Unit of the Perlis State Health Department.

Study Population and Eligibility Criteria

The study population comprised all individuals at PUSPEN Perlis who participated in the HCV screen-and-treat program between October 2022 and December 2023. The inclusion criteria for this study were: (i) adult aged 18 years or older who participated in the hepatitis C screen-and-treat program at PUSPEN Perlis, and (ii) having a confirmed diagnosis of hepatitis C based on a positive HCV RNA test result. Individuals were excluded if their anticipated duration of stay within the 6-month program was deemed insufficient for

Table I: Characteristics of participants with anti-HCV positive (N=62).

Characteristics	n	(%)
Age(mean, SD)	44.1	(6.64)
Age Group (years)		
20-29	2	(3.2)
30-39	14	(22.6)
40-49	34	(54.8)
50-59	12	(19.4)
Gender		
Male	62	(100.0)
Ethnicity		
Malay	57	(91.9)
Chinese	2	(3.2)
Indian	3	(4.8)
Risk Factor*		
People who inject drugs**	49	(79.0)
Previously in jail/prison	42	(67.7)
Tattooing	21	(33.9)
Partner who is HCV-infected	12	(19.4)
History of invasive medical procedures	10	(16.1)
Body piercing	8	(12.9)
Men who have sex with men	5	(8.1)
Sex worker	4	(6.5)
Recipient of blood/blood products before 1994	2	(3.2)
Number of risk factors		
1	21	(33.9)
2-4	37	(59.7)
>4	4	(6.4)
APRI score		
<1.5	62	(100)
≥1.5	0	(0)

* Participant can have more than one risk factor.
** People who inject drugs: Participants with any history of injection drug use (past or present).
Abbreviations: SD, standard deviation; APRI, Aspartate aminotransferase to Platelet Ratio Index.

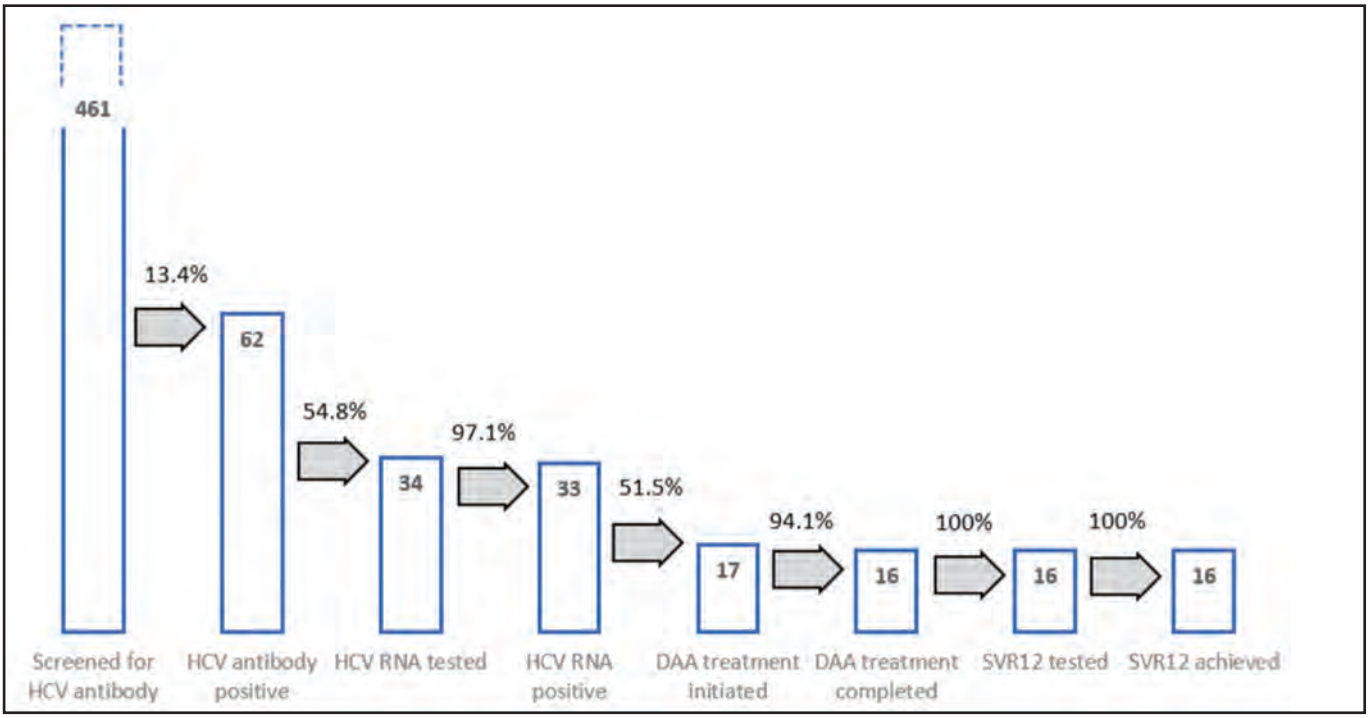

Fig. 1: Progression of participants in HCV screen-and-treat program at PUSPEN Perlis, Oct 2022– Dec 2023

the standard 12- or 24-week DAA treatment course and subsequent SVR12 follow-up assessment.

Data Collection

The relevant data for this study were retrospectively retrieved from the program's database. As the data were initially collected for program monitoring rather than research, the scope of information available for participants, particularly those undergoing initial screening, was limited. The information extracted included: (i) baseline characteristics of the program participants, such as age, gender, and documented history of exposure to HCV infection risk factors (e.g., injecting drug use); (ii) results of blood investigations pertinent to hepatitis C management (HCV RNA test results); (iii) DAA treatment history, including the date of treatment initiation, prescribed treatment duration, and treatment completion status; and (iv) treatment outcomes, specifically the achievement of SVR12, defined as an HCV RNA level below the limit of quantification (<15 IU/mL) at 12 weeks following the completion of antiviral therapy.

Statistical Analyses

The analysis of the study results primarily involves descriptive statistics to summarise the characteristics of the participants and the overall outcomes of the implemented screen-and-treat program. Categorical variables were presented as frequencies and percentages within each category. Numerical variables, including age, will be reported as means and standard deviations if the data are normally distributed, or as medians and interquartile ranges if the data exhibit a skewed distribution. The proportion of participants who underwent on-site anti-HCV RDT and subsequent HCV RNA testing were calculated. Further analysis of HCV RNA status was performed to those who underwent HCV RNA testing. Treatment uptake was analysed among participants with confirmed positive HCV RNA results. Treatment initiation and completion rates were determined for those who commenced antiviral therapy, and the SVR12 achievement rate were assessed for participants who completed treatment and underwent the post-treatment virological assessment.

RESULTS

Study population characteristics

During the study period, 461 participants who received drug rehabilitation at PUSPEN Perlis were screened, and 62 (13.4%) tested positive for HCV antibody. All those with positive HCV antibody were male, and the majority were Malay (91.9%). Their mean age was 44.1 years (SD=6.64), with over half (54.8%) aged 40-49 years. The majority reported at least two risk factors for HCV (66.1%), most commonly injection drug use (79.0%) and prior incarceration (67.7%). None of the participants had liver cirrhosis (APRI score ≥1.5), hepatitis B or HIV co-infection. Characteristics of participants underwent HCV screening test are summarised in Table I.

HCV screen-and-treat program's outcome

Among these 62 HCV antibody-positive participants, 28 (45.2%) did not proceed with confirmatory testing for HCV RNA detection, primarily due to anticipated short stays or difficulties in sample collection. Of those who underwent confirmatory HCV RNA testing, one (3.0%) had undetectable HCV RNA, while the vast majority (33, 97.0%) had positive HCV RNA, confirming active HCV infection (Figure 2). Subsequently, participants who tested positive for HCV RNA underwent pretreatment assessments, and none of them had liver cirrhosis (APRI score ≥1.5). However, only 17 (51.5%) initiated DAA treatment with sofosbuvir-daclatasvir combination for a planned duration of 12 weeks. The remaining 16 (48.5%) with positive HCV RNA did not commence treatment due to their anticipated short stays in the rehabilitation centre. During the treatment course, one participant who had started DAA therapy was transferred to another rehabilitation centre and was lost to follow-up for SVR12 assessment. The remaining 16 (94.1%) successfully completed the 12-week DAA treatment regimen and subsequently underwent SVR12 testing. Notably, all 16 participants (100%) who completed treatment had achieved SVR12 (100%). Furthermore, no adverse side effects were reported by any of the participants who received DAA treatment during the study period.

DISCUSSION

The implementation of a new screen-and-treat program for HCV within a drug rehabilitation centre in Perlis yielded notable insights into the feasibility and outcomes of HCV care delivery within this vulnerable population. Our study revealed a seroprevalence of HCV antibodies of 13.4% among individuals in PUSPEN Perlis during the study period, highlighting the significant burden of HCV infection within this setting, consistent with the elevated prevalence observed among people who inject drugs both regionally and globally.[5-7,14] Additionally, the significant burden of HCV infection within this rehabilitation centre is consistent with observations elsewhere.[15,16] For instance, a study in drug rehabilitation facilities in Japan reported a prevalence of 11.1% among residents.[15] This finding underscores the critical need for routine screening upon entry into drug rehabilitation facilities.

However, our findings also highlight several challenges in translating screening positivity into the full cascade of HCV care within this specific context. A substantial proportion (45.2%) of participants who screened positive for HCV antibodies did not proceed to confirmatory HCV RNA testing. This was primarily attributed to the screening activities being performed on existing residents, rather than on admission, which often led to an anticipated shorter duration of stay within the rehabilitation centre before participants completed their program. Additionally, practical difficulties in obtaining blood samples contributed to this gap. These factors emphasise the unique logistical constraints inherent in delivering healthcare within a residential rehabilitation setting, where the length of stay is predetermined, and medical procedures may face operational hurdles. To mitigate missed opportunities for treatment initiation due to short stays, it's crucial that HCV screening be conducted promptly upon admission to the centre. Streamlining the process for confirmatory testing and exploring alternative sampling methods that are less invasive and more readily implementable in this environment could potentially

improve the proportion of participants undergoing RNA testing. For instance, a 'one-stop-shop' model implemented in Australian prisons incorporated finger-stick point-of-care HCV RNA testing, which provided diagnostic results within one hour.[17,18] This approach was found to be beneficial, timely, and increased uptake of prisoners into the treatment pathway.

Among those who underwent confirmatory testing, the high rate of active HCV infection (97.0% of RNA-tested participants) further reinforces the necessity for targeted interventions. Despite this high prevalence of viraemic infection, only slightly more than half (51.5%) of those with detectable HCV RNA initiated antiviral treatment. The primary barrier to treatment initiation, similar to that observed for RNA testing, was the anticipated short duration of stay, deemed insufficient to complete the standard 12-week DAA regimen. This highlights a critical mismatch between the standard treatment duration and the typical length of stay for a significant portion of participants within the rehabilitation program. Exploring shorter duration DAA regimens, where clinically appropriate, or establishing robust referral pathways and linkages to care upon discharge, are crucial considerations to improve treatment uptake in this population. In line with exploring shorter options, an investigator-initiated trial has recently been completed for a potential 8-week DAA treatment combining sofosbuvir and ravidasvir (ClinicalTrials.gov ID: NCT04885855). The anticipated finding that this regimen is equivalent in efficacy and safety to the standard 12-week duration would be transformative for hepatitis C treatment, particularly in settings where shorter treatment windows are necessary, such as prisons and drug rehabilitation centres.

Despite the challenges in the initial steps of the care cascade, the treatment outcomes among those who initiated and completed therapy were highly encouraging. The 100% SVR12 rate achieved by the 16 participants who completed the 12-week DAA course is remarkable and consistent with the high efficacy of modern DAAs reported in various populations.[10,11] This finding demonstrates that when treatment can be initiated and completed within the rehabilitation setting, it can be highly successful in achieving viral eradication. This finding aligns with the notion to cure HCV among people incarcerated either in prison or a rehabilitation setting to achieve the WHO hepatitis elimination targets.[19,20] Furthermore, the absence of reported side effects among those treated suggests that DAA therapy was well-tolerated in this population.

The loss to follow-up of one participant due to transfer to another facility underscores the importance of inter-institutional communication and coordinated care for individuals within the rehabilitation system. Establishing mechanisms for seamless transfer of medical records and continuation of treatment across different facilities could help prevent attrition along the care pathway.

Our study has several limitations. The retrospective nature of the study and reliance on secondary data may introduce potential biases and limit the availability of detailed clinical information. Furthermore, the reasons for difficult blood taking were not systematically documented, which could provide valuable insights for future program improvements. The exclusion of participants with a stay of < 6 months also might have underestimated the overall impact of the program on the entire cohort of admissions. Importantly, the study population consisted exclusively of male participants (100%), which accurately reflects the current residents of this specific drug rehabilitation centre. This demographic constraint limits the generalisability of the identified psychosocial barriers and success factors to female PWID and the broader female high-risk population in Perlis State. Therefore, future HCV programs must actively seek tailored strategies and opportunities to engage female high-risk populations, possibly outside of single-gender centres, to ensure equitable progress toward national HCV elimination goals.

In conclusion, this study provides valuable real-world data on the implementation of an HCV screen-and-treat program within a drug rehabilitation centre in Malaysia. While the high HCV seroprevalence justifies the need for such programs, significant challenges remain in ensuring progression through the entire care cascade, particularly regarding confirmatory testing and treatment initiation, largely influenced by the duration of stay in the facility. The excellent treatment outcomes observed among those who completed therapy highlight the potential for HCV elimination within this population when these barriers can be overcome. Future efforts should focus on strategies to streamline diagnostic processes, particularly during the early phase of admission to the centre, explore shorter treatment durations, and establish effective linkages to care post-discharge to maximise the impact of HCV elimination programs within drug rehabilitation settings. Further research could also explore the cost-effectiveness of such integrated programs and the long-term impact on both individual health and public health outcomes within this marginalised population in Malaysia.

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ORIGINAL ARTICLE

Digital eye strain among library users: Prevalence and ROC-derived cut-off point for the DESRIL-27

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ABSTRACT

Introduction: Digital eye strain (DES), also known as computer vision syndrome, has become a growing public health issue among students due to prolonged screen exposure. Reliable, locally validated screening tools are essential to estimate prevalence and guide prevention. This study aimed to establish a receiver operating characteristic (ROC)-based cut-off for the Digital Eye Strain and Risk Level Questionnaire (DESRIL-27) against the Computer Vision Syndrome Questionnaire (CVS-Q) as the reference standard, and to estimate the prevalence of DES among university library users.

Materials and Methods: A cross-sectional study was conducted between June and September 2024 among users of Universiti Malaysia Sabah libraries. Participants completed the DESRIL-27 and CVS-Q via Microsoft Forms. Data were exported to Excel, cleaned, and analysed in RStudio (version 2025.05.1). Reliability was assessed using Cronbach's alpha. ROC analysis determined the optimal DESRIL-27 cut-off, and diagnostic performance was quantified using sensitivity, specificity, predictive values, and likelihood ratios. Prevalence was estimated based on the optimal threshold with 95% confidence intervals (CI). Ethical approval was obtained from the Medical Research Ethics Committee, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah (JKEtika 3/24 (8)).

Results: A total of 277 participants were included (mean age 24.2 years, 67% female). Internal consistency was excellent (α=0.964 for symptoms; α=0.921 for risk factors). ROC analysis yielded an area under the curve of 0.982 (95% CI: 0.970, 0.994). The optimal cut-off was ≥14.5, demonstrating sensitivity of 90.9% and specificity of 96.7%, with a positive predictive value of 98.3% and a negative predictive value of 83.8%. The likelihood ratios were LR+ =27.6 and LR– =0.09. At this threshold, the prevalence of DES was 62.1% (95% CI: 56.1, 67.8).

Conclusions: The DESRIL-27 demonstrated excellent reliability and diagnostic performance, with an empirically derived cut-off of ≥14.5. These findings support its use as a screening tool for digital eye strain in university settings.

KEYWORDS:
Asthenopia, digital eye strain, computer vision syndrome, ROC curve, Public Health, Universities, Cross-Sectional Studies, Prevalence

INTRODUCTION

Digital eye strain (DES), also known as computer vision syndrome (CVS), is increasingly recognized as a public health issue in the digital era. Prolonged exposure to a Visual Display Terminal (VDT), with as little as two continuous hours, can trigger Digital Eye Strain (DES) symptoms such as eye fatigue, dryness, blurred vision, headaches, and difficulty focusing. A VDT refers to any device that presents visual information including computers, laptops, tablets, smartphones or game console.[1–3] The global prevalence of DES ranges between 50% and 70%, depending on the population studied and the screening tool applied.[4,5] These symptoms can negatively affect productivity, academic performance, and overall quality of life.[2,6]

University students are particularly vulnerable due to prolonged screen exposure in educational and recreational settings. In Malaysia and other Southeast Asian countries, where digital learning environments have expanded rapidly, DES represents an important occupational and educational health concern.[7,8] Despite its burden, standardized and validated cut-off values for DES screening tools remain limited, especially for local populations.

Various questionnaires have been developed to identify DES. The Computer Vision Syndrome Questionnaire (CVS-Q) by Seguí et al., is among the most widely validated tools, serving as a reference standard across different populations.[9] More recently, the Digital Eye Strain and Risk Level 27-item scale (DESRIL-27) developed by a group of ophthalmologists in the Universiti Brunei Darussalam, has been introduced to capture both symptom severity and environmental or ergonomic risk factors.[10] Although DESRIL-27 has demonstrated high internal consistency (Cronbach's alpha >0.88) and acceptable construct validity, no validated cut-off score has been established, limiting its use for diagnostic screening.[10]

Establishing a reliable cut-off point is essential, as it transform a continuous symptoms score into meaningful classification of DES presence or absence. Traditional methods, such as using the mean ± standard deviation or percentile thresholds have used, but they may not accurately reflect diagnostic performance.[11,12] Receiver operating characteristic (ROC) curve analysis is widely recommended as a more robust method for identifying optimal thresholds, balancing sensitivity and specificity.[13]

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This study therefore aimed to determine the optimal ROC derived cut-off point for the DESRIL-27 symptom score in screening digital eye strain among university library users at the Universiti Malaysia Sabah, using the CVS-Q as the reference standard. The findings provide population-specific evidence to support the use of DESRIL-27 in local research, screening, and preventive practice.

MATERIALS AND METHODS

This study employed a cross-sectional analytical design and was conducted between June and September 2024 in two academic libraries at the Universiti Malaysia Sabah (UMS): the Main Library and the Medical Library. The Main Library receives approximately 1,000-1,500 visitors daily during regular academic periods, while the Medical Library receives 20-50 visitors. Both libraries provide access to common VDT-based equipment such as personal laptops, smartphones, and library desktop computers.

Study Instrument

For our study instrument, there are two validated questionnaires were administered through Microsoft Forms:
1.Digital Eye Strain and Risk Level Questionnaire (DESRIL-27) – a 27-item scale. There are two parts questionnaires: DES symptoms severity and Risk Level. The 15 DES symptom items are scored by multiplying frequency (0-2) and intensity (1-2), producing a continuous symptom score where higher values indicate greater severity. The remaining 12 items measure environmental and ergonomic risks, coded on a Likert-type response format and summed into a continuous risk score where higher value indicates higher risk.[10]

2.Computer Vision Syndrome Questionnaire (CVS-Q) developed by Seguí et al., which served as the reference standard for DES classification.9 The CVS-Q consist of 16 ocular symptoms; each rated for both frequency and intensity. Using established CVS-Q scoring Rules, symptoms are combined into a total score that is then dichotomised into DES categories. A total score of <6 indicates no DES, while score ≥6 indicates the presence of DES. This binary classification was used as the gold standard outcome for ROC curve analysis in this study.[9]

Both instruments were distributed in English versions, and informed consent was obtained prior to participation.

Study Population and Eligibility Criteria

The study population comprised students, staff and visitors who were actively using either of the two library facilities during data collection.
Inclusion criteria:
1. Individual using the library at the time of data collection.
2. Individuals who had engaged for at least two hours or more of continuous VTD use, consistent with recommendations from the American Optometric Association (AOA).[2] A VDT refers to any device that presents visual information including computers, laptops, tablets, smartphones or game console
3. Age ≥18 years.

Exclusion criteria:
1. Individuals with medical conditions affecting vision and requiring regular hospital follow-up.
2. Those declining to provide informed consent.

Sample Size Estimation

Sample size was calculated using Cochran's formula for a single proportion.1[4] Based on a previous study in Thai university students reporting an 81% prevalence of DES with a 95% confidence level (Z=1.96) and 5% precision (d=0.05), the minimum sample size was 238 participants.[15] After accounting for a 15% non-response rate, the final target sample size was 280 participants.[16]

Sampling Strategy and Data Collection Procedure and Management

A multistage sampling approach was applied, combining cluster, systematic, and purposive elements. The UMS Main Library and Medical and Hospital Library were divided into approximately 20 functional zones (reading areas, computer sections, discussion rooms, and librarian offices), which served as natural clusters. For the larger research project, these zones were observed repeatedly across different time slots and dates, resulting in 64 sampling occasions. This provides a systematic coverage of both spatial (library areas) and temporal variation (different dates and times), thereby minimizing selection bias. Such an approach ensured balanced recruitment across high- and low-traffic areas as well as different lighting conditions, strengthening the representativeness of the study population. Minimal missing sociodemographic data were addressed using mean substitution to reduce attrition bias. On each sampling occasion, 5-10 participants were purposively approached within the designated zone based on availability. Individuals who had already completed the survey on earlier occasions were excluded to avoid duplication. Eligible participants were given a participant information sheet, and digital informed consent was obtained prior to survey completion.

The questionnaire was completed via a Microsoft Form, accessible through a QR code or direct link. Participants used their own devices (smartphones, tablets, or laptops) to answer the survey while seated in the library. Each session took approximately 3-7 minutes per participant. Researchers remained present during the sessions to clarify queries and to ensure independent completion. All responses were automatically stored in a secure Microsoft database accessible only to the research team

Survey responses were automatically stored in Microsoft Forms and exported in Excel format. Raw data were cleaned and coded in Microsoft Excel during the first stage of data preparation. Statistical analyses were then conducted in RStudio (version 2025.05.1, Build 513; R Foundation for Statistical Computing, Vienna, Austria). Because the Microsoft Form required participants to answer each item before proceeding, the DESRIL-27 and CVS-Q datasets were complete. Only sociodemographic variables (age, height, and weight) had minimal missing values (n=12), which were replaced with mean values.

Table I: Diagnostic Classification of DESRIL-27 Against CVS-Q (2x2 table)

DESRIL-27 (Cut-Off 14.5)	CVS-Q Positive	CVS-Q Negative	Total
Positive (≥14.5)	169 (TP)	3 (FP)	172
Negative (<14.5)	17 (FN)	88 (TN)	105
Total	186	91	277

Table II: Diagnostic Performance of DESRIL-27 at Multiple Cut Off Scores

Cut-Off Score	Sensitivity	Specificity	PPV	NPV	Youden Index
12	98.4%	62.6%	84.4%	94.0%	0.61
13	96.8%	74.7%	89.4%	91.9%	0.72
14	93.5%	87.9%	95.6%	84.7%	0.81
14.5 (Optimal)	90.9%	96.7%	98.3%	83.8%	0.88
15	88.2%	97.8%	98.8%	81.5%	0.86
16	82.8%	98.9%	99.2%	77.2%	0.82
17	79.0%	99.0%	99.2%	74.8%	0.78

Table III: Sociodemographic characteristics by DES status and Risk-Level Scores

Characteristic	n (%)	DES Present n (%)	DES Absent n (%)	Mean RL Score ± SD
Age Group				
18–24 years	188 (67.9%)	124 (66.0%)	64 (34.0%)	12.3 ± 5.7
25–34 years	67 (24.2%)	39 (58.2%)	28 (41.8%)	12.9 ± 6.0
≥35 years	22 (8.0%)	9 (40.9%)	13 (59.1%)	13.2 ± 6.4
Sex				
Male	91 (32.9%)	41 (45.1%)	50 (54.9%)	11.7 ± 5.6
Female	186 (67.1%)	131 (70.4%)	55 (29.6%)	13.0 ± 5.8
Screen Time (VDT hours)				
<2 hours/day	42 (15.2%)	15 (35.7%)	27 (64.3%)	10.8 ± 4.9
2–4 hours/day	157 (56.7%)	102 (65.0%)	55 (35.0%)	12.4 ± 5.7
>4 hours/day	78 (28.2%)	55 (70.5%)	23 (29.5%)	14.5 ± 6.3
Total	277 (100%)	172 (62.1%)	105 (37.9%)	12.5 ± 5.8

Statistical Analysis

Descriptive statistics were summarised using means, standard deviations (SD), medians, interquartile ranges (IQR), and frequencies where appropriate. Internal consistency reliability of the DESRIL-27 symptom and risk subscales was assessed using Cronbach's alpha. Receiver operating characteristic (ROC) curve analysis was performed using the CVS-Q dichotomous classification as the reference standard. The area under the curve (AUC) and its 95% confidence interval were calculated. Optimal cut-off points were determined using Youden's index and the closest-to-top-left method. Diagnostic performance metrics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed at the optimal threshold. The ROC-derived cut-off was then used to estimate the prevalence of DES in the study population.

Ethical Approval

This study was approved by the Medical Research Ethics Committee, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah (Approval Code: JKEtika 3/24 (8)). Participation was voluntary, and informed consent was obtained from all participants prior to data collection. Confidentiality and anonymity of responses were assured throughout the study

RESULTS

Participant characteristics

A total of 277 participants were included in the analysis. The mean age was 24.2 years (SD 6.3). The majority were female (67%), while 33% were male. The mean body mass index (BMI) was 23.7kg/m² (SD=5.4). All participants reported using at least one digital device during library use, primarily smartphones and laptops with average screen exposure of 6.3 hours per day (SD=2.4)

DESRIL-27 score distribution

The overall DES score had a mean of 29.9 (SD=27.7), with a median of 21 and an interquartile range (IQR) of 37. Scores ranged widely from 0 to 171, reflecting substantial variability in symptom severity among participants. The RL score had a mean of 12.5 (SD=5.8), with a median of 12, IQR of 4, and a range of 0-33.

When participants were classified using the ROC-derived threshold (≥14.5), the mean DES score among those without DES (n=105) was 6.2 (SD=4.7), compared to 44.5 (SD=25.8) among those with DES (n=172).

DESRIL-27 scale internal consistency

Internal consistency reliability of the DESRIL-27 was excellent. Cronbach's alpha for the Symptoms subscale was 0.964 (standardized α=0.965), and for the Risk Level subscale

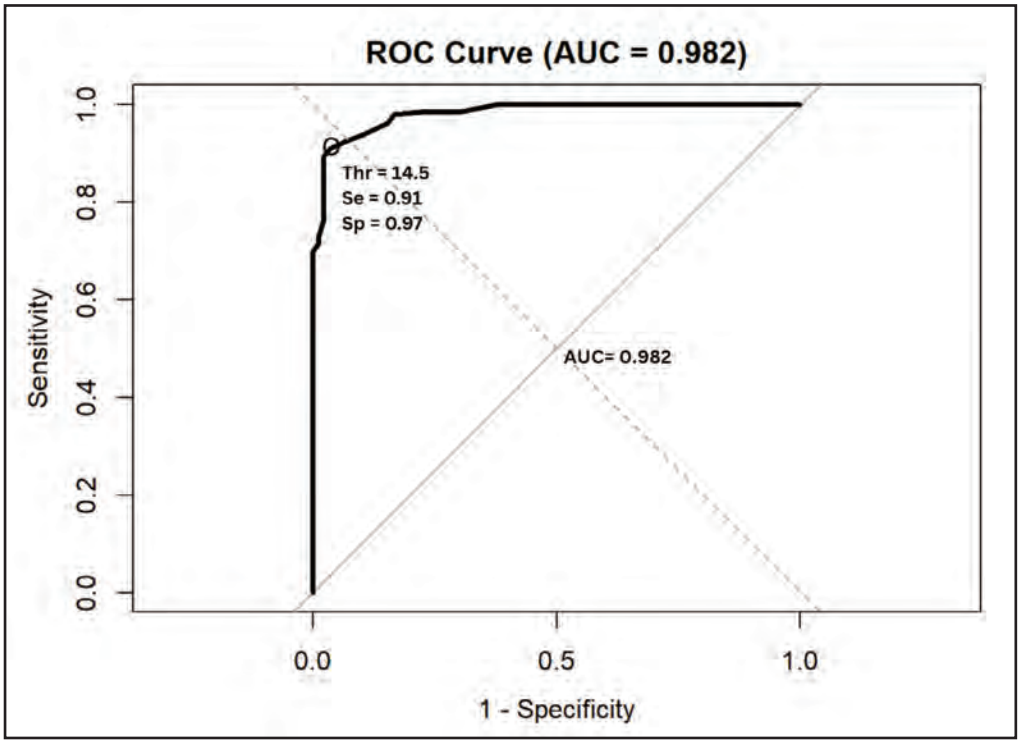

Fig. 1: ROC of DES score using CV-Q as reference with threshold value at 14.5.

0.921 (standardised α=0.925). Overall, the DESRIL-27 scale was 0.972 (standardised α=0.973). Although Cronbach's alpha values exceeded 0.90, suggesting strong coherence among items, they may also indicate potential redundancy, where several items measure highly similar construct.

ROC analysis and diagnostic performance

Assumption checks confirmed that the DESRIL-27 symptom scores were suitable for non-parametric ROC analysis, with clear distributional separation between CVS-Q groups, appropriate predictor directionality, and fulfilment of the binary outcome requirement.

Visual inspection of histograms showed that DESRIL-27 symptom scores were right-skewed within both CVS-Q–positive and CVS-Q–negative groups; therefore, a non-parametric ROC analysis (DeLong method) was used.

The DESRIL-27 symptoms score showed excellent ability to discriminate CVS-Q–defined DES cases from non-cases. The area under the ROC curve (AUC) was 0.98 (95% CI 0.970, 0.994). Using the CVS-Q classification as the reference standard and applying Youden's index, a cut-off value of ≥14.5 on the DESRIL-27. Figure 1 presents the ROC curve, with the optimal cut-off point (score 14.5) marked on the curve together with its corresponding sensitivity and specificity.

At this threshold (symptom score ≥ 14.5 indicating DES), the diagnostic performance was:

- Sensitivity: 90.9% (169/186; 95% CI 85.8, 94.4)
- Specificity: 96.7% (88/91; 95% CI 90.7, 99.0)
- Positive predictive value (PPV): 98.3% (169/172; 95% CI 94.9, 99.4)
- Negative predictive value (NPV): 83.8% (88/105; 95% CI 75.8, 89.5)

The corresponding 2×2 contingency table comparing DESRIL-27 (cut-off 14.5) with CVS-Q status is shown in Table I. In brief, there were 169 true positives, 88 true negatives, 3 false positives and 17 false negatives. From these estimates, the likelihood ratios were:

- Positive likelihood ratio (LR+): 27.6 (95% CI 9.0, 83.9)
- Negative likelihood ratio (LR–): 0.09 (95% CI 0.06, 0.15)

These values indicate that a positive DESRIL-27 result at ≥14.5 greatly increases the post-test probability of DES, while a negative result substantially reduces it. To allow flexibility in choosing alternative screening thresholds, diagnostic performance at adjacent cut-off values (12, 13, 14, 14.5, 15, 16, and 17) is summarised in Table II. Sensitivity decreased and specificity increased as the cut-off was raised, with the 14.5-15 range providing the best overall balance for screening purposes.

Prevalence of DES

Applying the ROC-derived threshold of ≥14.5, the overall prevalence of digital eye strain (DES) among library users was 62.1% (172/277; 95% CI: 56.1, 67.8). Female participants showed a higher proportion of DES cases compared to males (70.4% vs. 45.1%), reflecting their greater representation in the sample. DES was most common among younger users aged 18–24 years (66.0%), and prevalence increased with longer screen exposure, rising from 35.7% among those using

screens for less than 2 hours per day to 70.5% among those exceeding 4 hours. Table III describe the sociodemographic characteristic by DES status and Risk- Level Scores.

DISCUSSION

This study is among the first in Malaysia to validate and apply the Digital Eye Strain and Risk Level Questionnaire (DESRIL-27) in a university library setting. The DESRIL-27 demonstrated excellent internal consistency, with Cronbach's alpha values well above the conventional threshold of .70 recommended for psychological and health-related instruments.[17] Its discriminative ability against the Computer Vision Syndrome Questionnaire (CVS-Q) reference standard was exceptionally strong, with an AUC of .982. Using ROC analysis, we identified an empirically derived cut-off score of ≥14.5 that produced high sensitivity and specificity, indicating a substantial digital eye strain (DES) prevalence of 62.1% in this population.

The high reliability coefficients observed across both symptom and risk domains suggest that DESRIL-27 is a stable and internally coherent instrument for assessing DES risk. Although Cronbach's alpha values above .90 are often interpreted as excellent consistency, they may also reflect item redundancy, suggesting the possibility of future refinement to shorten the instrument without compromising diagnostic performance. These findings are consistent with earlier validation work on DESRIL-27, which also demonstrated strong internal consistency and robust psychometric characteristics.[10,18] Together, the evidence indicates that DESRIL-27 is well-suited for large epidemiological studies and may have utility as a clinical or occupational screening tool once further implementation pathways are developed.

The observed DES prevalence of 62.1% aligns with global estimates that range from 50-90% among university students and young adults.[1,19,20] It is somewhat lower than the 81% reported among Thai university students during virtual learning, highlighting how prevalence varies with differences in learning modalities, digital workloads, and contextual exposures.[15] Importantly, our data were collected in 2024, after the transition back to hybrid and in-person learning, yet DES remained common suggesting that the increase in digital dependence that occurred during the COVID-19 pandemic has persisted.[18,21,22] This underscores DES as an emerging and ongoing public health concern rather than a transient pandemic-related phenomenon.

The ROC-based cut-off of ≥14.5 demonstrated high diagnostic accuracy. In practical screening contexts, the high positive predictive value (PPV) indicates that most students scoring above this threshold are true DES cases, while the negative predictive value (NPV) suggests that a small proportion of symptomatic individuals may not be detected. These predictive values provide important context for decision-making in university settings: the cut-off can be applied as a first-stage screening tool to identify students requiring targeted ergonomic advice, behavioural interventions, or referral for optometric assessment. The CVS-Q remains a well-established reference standard,[9] but its binary classification system does not capture symptom severity or ergonomic risks. In contrast, DESRIL-27 incorporates symptom frequency, intensity, and environmental factors such as lighting, posture, and viewing distance factors known to influence DES.[23,24]

Although the focus of this paper was on validating the symptom component and establishing a diagnostic cut-off, the risk-level component of DESRIL-27 remains an important part of the instrument. While risk-level data were collected, we did not proceed with full analysis of this component because ergonomic risk evaluation typically requires assessment by a trained and competent ergonomics professional, using standardised ergonomic tools as the gold standard for comparison. Specialised assessment such as workstation observation, lighting measurement, posture scoring, and viewing-distance evaluation was beyond the expertise and scope of the study team.[25,26] Without a recognised gold standard for ergonomic risk assessment in the study setting, it was not methodologically appropriate to validate or compare the DESRIL-27 risk-level scoring system. Future studies incorporating expert ergonomic assessment would allow the risk-level domain to be more rigorously evaluated and interpreted.

This study's multistage sampling approach, which included participants from different library zones at various times of day, provides ecological validity by capturing variation in lighting, seating, device type, and study behaviours. Although zone-specific and temporal analyses were beyond the scope of the present paper, this sampling design establishes a foundation for future work to identify high-risk library environments or peak periods associated with increased DES. Descriptive trends observed in this study for example, higher DES scores among younger students, those with higher BMI, and those with longer screen exposure mirror findings from Jordan, Saudi Arabia, and Malaysia.[27–29] Nonetheless, the cross-sectional design precludes causal inference, and unmeasured factors such as refractive error, sleep quality, and stress may also influence symptom reporting.

Strengths of this study include systematic sampling across 20 library zones, the inclusion of different time periods to reduce temporal bias, and the use of a validated reference tool for ROC analysis. The ROC methodology followed established recommendations for determining optimal thresholds.[11,13] Missing data were minimal and handled by mean replacement, a pragmatic method that may slightly reduce variability but was unlikely to meaningfully affect diagnostic performance. A limitation is that only one university library population was sampled, which may restrict generalisability to other settings such as secondary schools, office workplaces, or clinical populations. Additionally, the ergonomic risk component was not deeply analysed, and observational ergonomic assessments were not conducted, limiting interpretation of risk-level influences.

Despite these limitations, the findings provide strong preliminary evidence that DESRIL-27 is a reliable and valid tool for estimating DES in Malaysian university settings. The high prevalence of DES highlights the need for preventive

strategies rooted in digital health promotion. Universities can incorporate DESRIL-27 into wellness screening initiatives, apply the ≥14.5 threshold to flag students at risk, and deploy targeted interventions such as the 20-20-20 rule, scheduled micro-breaks, visual hygiene education, and ergonomic improvements in study spaces.[30,31] Future studies should analyse the risk-level subscale in detail, conduct stratified and longitudinal analyses, and test integration of the tool into student health services to support early identification and management of DES.

CONCLUSION

This study provides strong evidence that the DESRIL-27 is a reliable and valid instrument for assessing digital eye strain among Malaysian university students, demonstrating excellent internal consistency and exceptional discriminatory performance against the CVS-Q reference standard. The empirically derived cut-off score of ≥14.5 effectively identified a high prevalence of DES, underscoring the growing public health relevance of digital visual symptoms in post-pandemic academic environments. Although the risk-level component could not be fully evaluated due to the need for expert ergonomic assessment and absence of a gold standard comparison, the findings highlight the potential of DESRIL-27 as a practical screening tool for universities to identify at-risk students and guide early preventive measures. Future research incorporating competent ergonomic evaluation, longitudinal follow-up, and application across diverse settings will further strengthen the instrument's utility and support the development of comprehensive digital eye health strategies.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Epidemiology of major trauma in Malaysia: Preliminary findings from the Malaysian Trauma Registry

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ABSTRACT

Introduction: Epidemiological data regarding major trauma in Malaysia is limited due to the unavailability of a sustainable trauma registry (TR). Recognising its importance, a national TR known as the Malaysian Trauma Registry (MTR) was established in 2020. This study aims to investigate the epidemiology of major trauma in Malaysia utilising data from the MTR.

Materials and Methods: A retrospective analysis of the MTR data from 1st January 2021 to 30th April 2024 was conducted. This study focused on major trauma patients who presented at the participating hospitals or were transferred from other healthcare facilities and met the MTR enrolment criteria. A total of 2774 patients were included in the analysis.

Results: The most frequently affected group by major trauma was young males aged 15-44. Road traffic accidents (RTAs) were the leading cause of injury, followed by falls. More than half of the patients arrived at the hospital via ambulance, with a median time of 45 minutes from the emergency call to hospital arrival. In the emergency department (ED), nearly 80% of the patients were treated in a shared resuscitation bay, and the trauma team was activated for only one-third of cases. The most common type of Computed Tomography (CT) performed was CT brain. The median time from arrival to first CT was 95 minutes. Approximately 19.5% of patients were directly sent from the ED to the operating theatre for emergency surgery, while 19.6% required admission to the intensive care unit. The head and neck were the most frequently injured body regions (31.7%), with the head and thorax having the highest severity according to the Abbreviated Injury Scale. The median Injury Severity Score was 13 (IQR 7-19), and the median length of hospital stay was 4.4 days (IQR 1.9-10.6 days). The in-hospital mortality rate was 10.9%, with the highest rates observed among young males aged 15-44 and those involved in RTAs.

Conclusion: This study has highlighted the burden of major trauma and provided insight into the current quality of trauma care in Malaysia. The information gathered will be used to understand the standard of the existing trauma system and assist in designing trauma care enhancement plans.

KEYWORDS:
Epidemiology, trauma registry, major trauma, Malaysia

INTRODUCTION

The World Health Organization (WHO) stated that 4.4 million people die every year due to trauma worldwide.[1] The majority of trauma-related deaths occur in developing countries and commonly involve the young population.[1] The rate of trauma mortality is inversely related to the economic level of a country.[2] Approximately one-third of mortalities can potentially be avoided with a better trauma care system and effective preventive measures.[3] Evidence shows that trauma puts a significant burden on the developing nation's economy due to substantial loss of productivity years and financial capital due to high medical care costs.[1] Malaysia is a developing Southeast Asian country with a total population of 33.4 million.[4] Trauma is the sixth leading cause of hospital admissions, and road traffic accidents (RTA) have been identified as one of the top five causes of death in Malaysia.[5,6] It is the principal cause of total disease burden for children between 5 and 14 years old and young adults between 15 and 29 years old, with Disability-Adjusted Life Years of 9.3%(21 913) and 23.5% (180 031) respectively.[7]

A trauma registry (TR) is a structured database that records information regarding injured patients, including demographics, injury events, prehospital care, in-hospital care, diagnosis, and outcomes.[8,9] It is an effective tool to study injury surveillance, implement preventive strategies, strategise resource allocation, and develop quality improvement programs through clinical research and audits.[9,10] High-income countries (HICs) have proven that information gathered from comprehensive TR has greatly impacted the development of a better trauma care system, leading to a reduction in mortality and morbidity.[11] Establishing TR in a few developing countries has brought positive changes in trauma care.[12,13] An ideal TR should have a specified population, a dedicated management team, and a comprehensive data collection system to enable accurate data analysis, reporting, and validation.[14] Most developing countries do not have a structured nationwide TR.[15] One of the main obstacles is the high maintenance cost.[16] Lack of support from the stakeholders, human resource limitations, limited infrastructure, and lack of awareness regarding the importance of TR are among the other problems.[10] In

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developing countries, trauma-related data are commonly extracted from hospital-based patient information systems or short-term databases set up for research purposes.[17,18] Among the 115 countries that regularly report health statistics to the WHO, only 29 were found to have a national TR.[19,20] A literature review revealed that almost all the publications derived from TR originated from HICs, while the Southeast Asia region, where Malaysia is located, had the least number of publications.[21]

Epidemiological data on major trauma in Malaysia are scarce and inconsistent due to the absence of a sustainable TR. It was last reported in the year 2009.[22] The report was generated from the National Trauma Database (NTrD), which had to be discontinued in the year 2010 due to a lack of financial support.[23] The data collected were from 5 hospitals located within the same state; thus, it did not represent the overall epidemiology in Malaysia. Only essential variables which concentrated on in in-hospital management were included in the NTrD. This is typical of developing country registries, which collect fewer variables and are less stringent on inclusion criteria.[21] Several other temporary hospital-based registries existed, but the data collected only represented the hospital's locality.[24] Due to various setbacks, data regarding trauma in Malaysia heavily depend on the Royal Police Force and Malaysian Institute of Road Safety Research databases, which only include data regarding RTA and do not contain clinical information. Recognising the importance of a TR, the Ministry of Health Malaysia (MOH) launched a new initiative in late 2020 to establish a nationwide TR known as the Malaysian Trauma Registry (MTR). Initially involving eight public hospitals, it was later expanded to 31 hospitals.

The overall aim of this study is to investigate the epidemiology of major trauma in Malaysia by utilising the information from the MTR, which has never been reported before. The specific objectives are: to define the demographics and injury characteristics of major trauma patients; to identify the clinical interventions and resources utilised to manage major trauma patients; and to describe the outcomes associated with major trauma patients. The primary outcome is to determine the rate of in-hospital major trauma-related mortality. The secondary outcome is to determine the in-hospital morbidity associated with major trauma.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of the MTR database between 1st January 2021 and 30th April 2024 involving 31 participating hospitals. Ethical approval for this study was granted by the Medical Research and Ethics Committee (MREC) of the MOH (NMRR ID: IF-23-03616-LWA).

Study setting and population

This study included all major trauma patients who presented to the Emergency Department Critical Zone (EDCZ) of the participating hospitals or were transferred from other health facilities and fulfilled the criteria for enrolment into the MTR. The criteria for enrolment in this study require the presence of any one of the following inclusion criteria: trauma patients who were triaged to the EDCZ, trauma patients who required mechanical ventilation, trauma patients admitted to the Intensive Care Unit (ICU) or High Dependency Unit (HDU) for > 24 hours, or trauma patients with an Injury Severity Score (ISS) >12. On the other hand, patients meeting any of the exclusion criteria will not be enrolled. These include trauma patients who are first admitted to the hospital >24 hours after the injury, trauma patients declared dead before arrival at the hospital, or trauma patients who arrive at the hospital with no signs of life and fail to respond to initial resuscitation efforts.

Data collection

MTR is an online web-based registry that was developed and managed by the Health Informatics Centre (HIFC), MOH. The registry consists of eight sections: demographics, injury event, out-of-hospital care, emergency trauma care, further management, injury pattern, outcome, and submission validation. MTR data is stored in a secure online cloud storage. Data entry is carried out by trained personnel at each hospital. Trained personnel trace the medical records of all trauma patients triaged to EDCZ, select eligible patients, extract the required information, and enter them into the registry. Centralised training is held annually. Additional technical support is provided through email and messaging application groups. A request for data transfer with details of the required variables was submitted to the HIFC. Upon approval, the HIFC released and shared the data. The shared data was filtered by removing duplicates and incomplete data before being enrolled in this study.

Statistical analysis

Data variables were arranged and analysed using International Business Machines Statistical Package for the Social Sciences version 29. Descriptive statistics were used to summarise the sociodemographic characteristics of subjects. Categorical data were expressed as percentages and evaluated using the Pearson chi-square test, where all tests were conducted at an α-level of 0.05.

RESULTS

A total of 2,774 completed data points were included for final analysis. Among 31 participating hospitals, Hospital Bintulu, located in East Malaysia, contributed the highest number of completed data (n=397,14.3%) (data not shown).

Demographics

Overall, 82.5% (n=2289) of the patients were males, and 17.4%(n=483) were females. The vast majority, 90.8% (n=2517), were Malaysian citizens. Specifically, the young population was most affected, with a median age of 32 (IQR 21-49) (Table I).

Type, Intention, Mechanism and Location of Injury

The dominant type of injury was blunt injury (95.6%,n=2615) in comparison to penetrating injury (4.4%, n=120). Most of the injury occurred unintentionally (84.6%, n=2328). The top three mechanisms of injuries in descending order were RTA (78.3%, n=2161), falls (9.8%, n=273), and injury by sharp objects (3.0%, n=85) (Table I). RTA was the

most common among the age group 15-44 in both genders (Fig 1A). Fall was frequently seen in males within the age group of 30-44, while in females, it was prevalent among the older age group (Fig 1B). The most typical location of injury was road (80%, n=2196), followed by home (9.8%, n=270), industrial factories (2.4%, n=66) and others.

Prehospital Care (PHC)
The most common mode of arrival to the hospital was via ambulance (n=1790,65.2%). Non-ambulance mode of arrival was 19% (n=523). Approximately one-third of the patients were attended by a Level III Advanced Life Support (ALS) provider (n=841,31.1%). Only half (53%, n=1437) of the prehospital triagings were to EDCZ. The median time interval between an emergency call and ambulance arrival at the hospital was 45 minutes (IQR 30-63 minutes).

Emergency Department (ED) Care
Direct admission from the scene comprised approximately two-thirds (63.3%, n=1726) of total admissions and the remaining were transferred cases. There was minimal variation in the rate of admission on different days of the week. Upon arrival, almost all patients (99.3%, n=2754) were triaged to EDCZ.

More than three-quarters of patients were treated at the shared resuscitation bay (78.7%, n=2151), followed by the dedicated trauma bay (8.5%, n=233), dedicated trauma service (7.4%, n=201) and unknown/unavailable (5.4%, n=189). Trauma team activations were initiated for 873 (32%) patients. Only 897 (33.2%) patients were attended by specialists or consultants upon arrival.

First ED Vital Signs
Median systolic blood pressure was 91 mmHg (IQR 78-108), median heart rate (HR) was 75 beats per minute (IQR 64-86), median respiratory rate was 20 per minute (IQR 18-22), median oxygen saturation was 99% (IQR 97-100) and median Glasgow Coma Scale (GCS) was 15 (IQR 12-15).

ED Intervention
Five most common interventions in ED were cervical collar application (62.9%, n=1746), tranexamic acid administration (45.6%, n=1266), rapid sequence intubation (28.6%, n=791), limb immobiliser application (22.9%, n=635) and blood transfusion (20.4%, n=567).

Radiological Imaging in ED
Extended Focused Assessment Sonography in Trauma (eFAST) was the most common imaging done in the ED, comprising 2496 (90%) patients. The most frequently performed X-ray was Chest X-ray (n=2429, 87.6%). The most common Computed Tomography (CT) performed was CT brain (n=1842, 66.4%). Only 121 (4.4%) patients underwent Whole-Body CT (WBCT).

Time Interval Between Hospital Arrival and First CT
Median time elapsed between hospital arrival and first CT was 95 minutes (IQR 50-163 minutes).

Emergency Surgical or Interventional Radiology (IR) Intervention
Overall, 19.5% (n=414) of patients were sent directly from ED to operation theatre (OT) for emergency surgical intervention. In contrast, only 0.6% (n=16) of patients were sent to the IR suite. The most common emergency surgical intervention performed in OT was pelvic external fixation (n=215, 8.1%), followed by damage control laparotomy (n=77, 2.9%), craniotomy (n=59, 2.9%) and others (n=63, 2.5%).

ED Length of Stay (LOS)
Median ED LOS was 6 hours (IQR 3 hours 58 minutes – 8 hours 50 minutes).

Level of In-Patient Care
During their hospital stay, 612 (22.1%) patients required surgery in OT, 146 (5.3%) required admission to HDU and 545 (19.6%) required admission to ICU.

Injury Severity
The five most frequently injured body regions were head and neck (51.8%), extremities and pelvic girdle (40.2%), thorax (28.7%), face (23.3%) and abdomen (16.9%). The majority of patients had mild to moderate injuries defined as Abbreviated Injury Scale (AIS) scores 1 and 2. The highest proportion of severe injuries (AIS 3 and above) was observed in the head, thoracic and lower extremity regions (Fig 2).

Overall, the median Injury Severity Score (ISS) was 13 (IQR 7-19) and the median New ISS was 16 (IQR 9-24). The greatest proportion of patients had an ISS of less than 16 (n=1362, 59.8%) (Fig 3).

Hospital LOS
Overall, the median hospital LOS was 4.4 days (IQR 1.9-10.6 days). Median hospital LOS was found to be directly proportional to the ISS.

Patient Outcome
In total, 86.3% (n=2395) of patients survived to discharge, while 10.9% (n=301) died (Fig 4A). The highest mortality was seen in the age group 15-44, and mortality was consistently higher among males across all age groups (Fig 4B). RTA recorded the highest mortality (76.4%, n=230) followed by fall (10.6%, n=32). Mortality due to RTA was most pronounced in the age group 15-44, whereas mortality due to fall was highest in those who were 60 years old and above. Mortality rate was found to be directly proportional to ISS (Fig 4C).

Among the survivors, 75.5% (n=1866) had a good recovery upon hospital discharge based on the Glasgow Outcome Scale Score. Most of the survivors (83.4%,n=2063) were discharged home, 8.0% (n=197) were transferred to another health facility, and only 1.0% (n=24) were referred to a rehabilitation centre.

Table I: Demographics and mechanism of injury

Demographics and mechanism of injury	Frequency (n)	Percentage (%)
Sex		
Male	2517	82.5
Female	483	17.4
Age Group		
0-14	220	7.9
15-29	1041	37.6
30-44	656	23.7
45-59	435	15.7
60-74	304	11.0
>75	113	4.1
Type of Injury		
Blunt	2615	96.6
Penetrating	120	4.4
Mechanism of Injury		
Road Traffic Accidents	2161	78.3
Falls	273	9.8
Injury by sharp objects	85	3.0
Injury by blunt object	55	2.0
Self-harm	40	1.4
Industrial/Construction	32	1.2
Unknown	34	1.2
Others	28	1.0
Blast/Explosion Injury	20	0.7
Animal Inflicted	17	0.6
Recreation related injury	9	0.3
Firearms injury	4	0.1
Electrocution	3	0.1

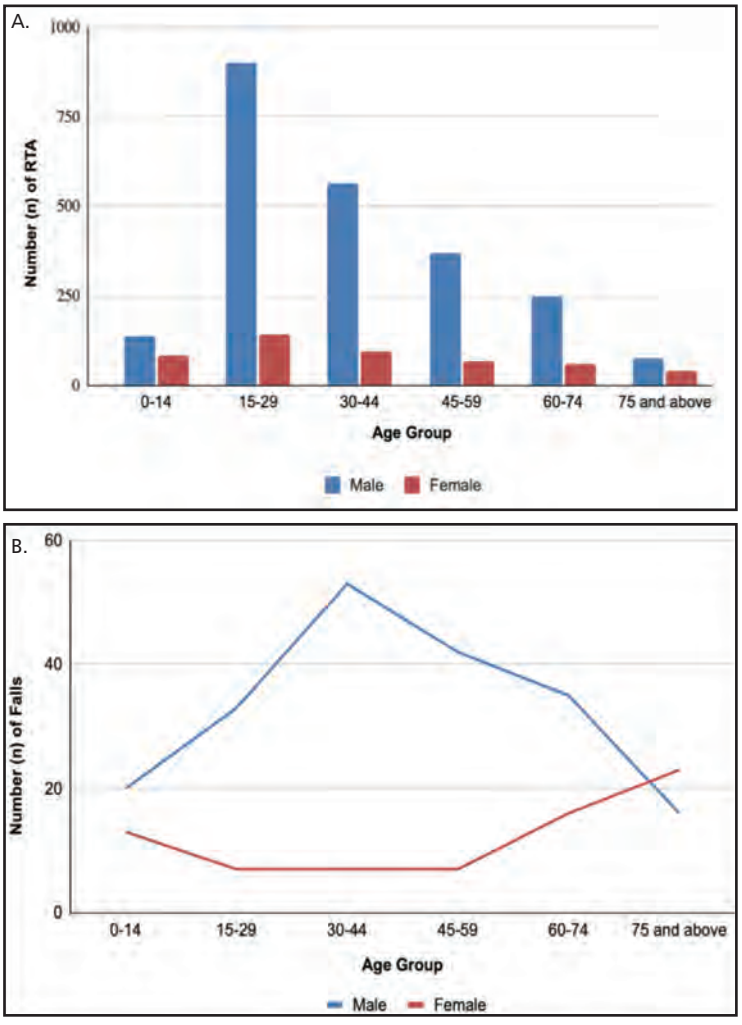

Fig. 1: A. Frequency of RTA by age group and gender. B. Frequency of fall by age group and gender.

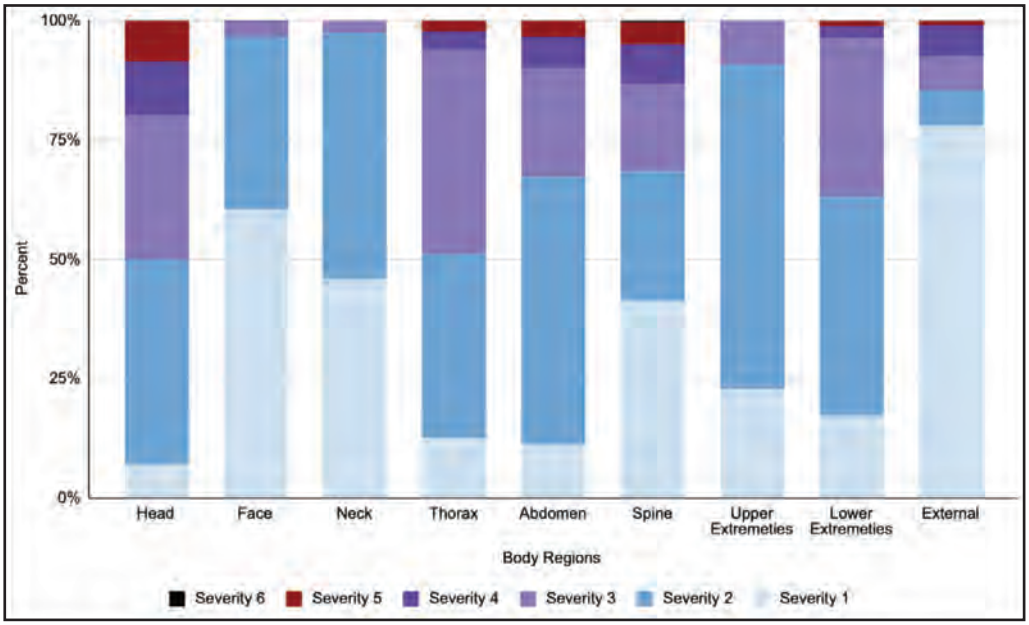

Fig. 2: AIS severity by body region

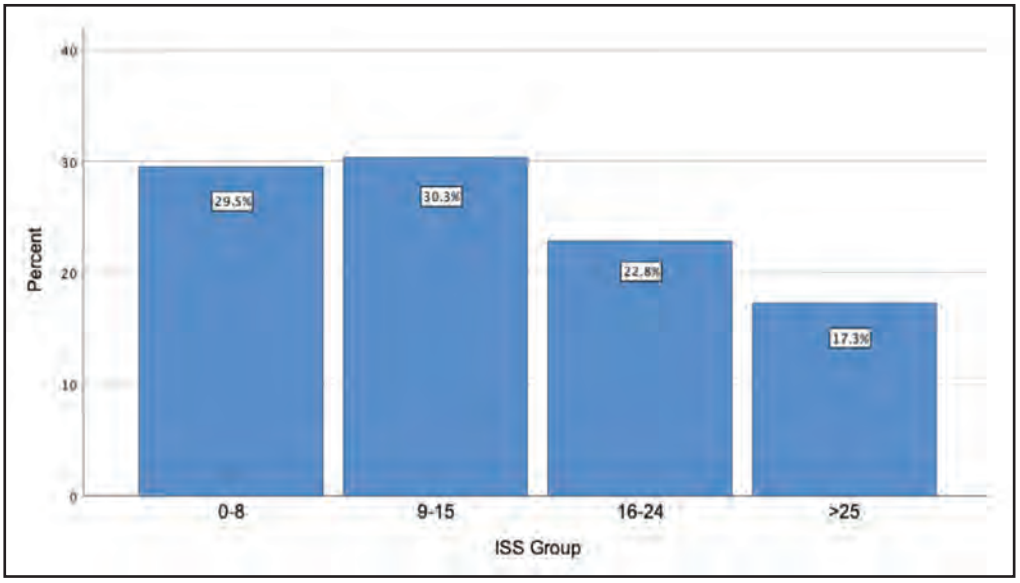

Fig. 3: Injury Severity Score (ISS) Distribution

DISCUSSION

This is the first report generated from the MTR database since it became operational in late 2020. The results provided an initial overview of the epidemiology of major trauma in Malaysia, detailing the demographics, injury mechanisms, injury characteristics, prehospital and in-hospital management, and patient outcomes.

Among the 31 hospitals participating in the MTR, only nine contributed a significant number of data. Fortunately, these hospitals are spread across different regions of the country, representing diverse populations and geographical variations. The disparity in data contribution is not unexpected, as most MTR personnel must multitask between clinical duties and managing the MTR database, significantly limiting their time for data entry. Additionally, managers typically prioritise clinical duties over non-clinical tasks, a common scenario in healthcare organisations within developing countries. Assigning a dedicated team for data management is not feasible in resource-limited settings, explaining the insufficient data entry volume among participating hospitals.

Besides the volume of data entry, data completeness was another significant issue, with the MTR data completion rate at only 58.5%. This low rate is likely due to the difficulty in searching for and extracting the necessary information, stemming from incomplete documentation in clinical notes,

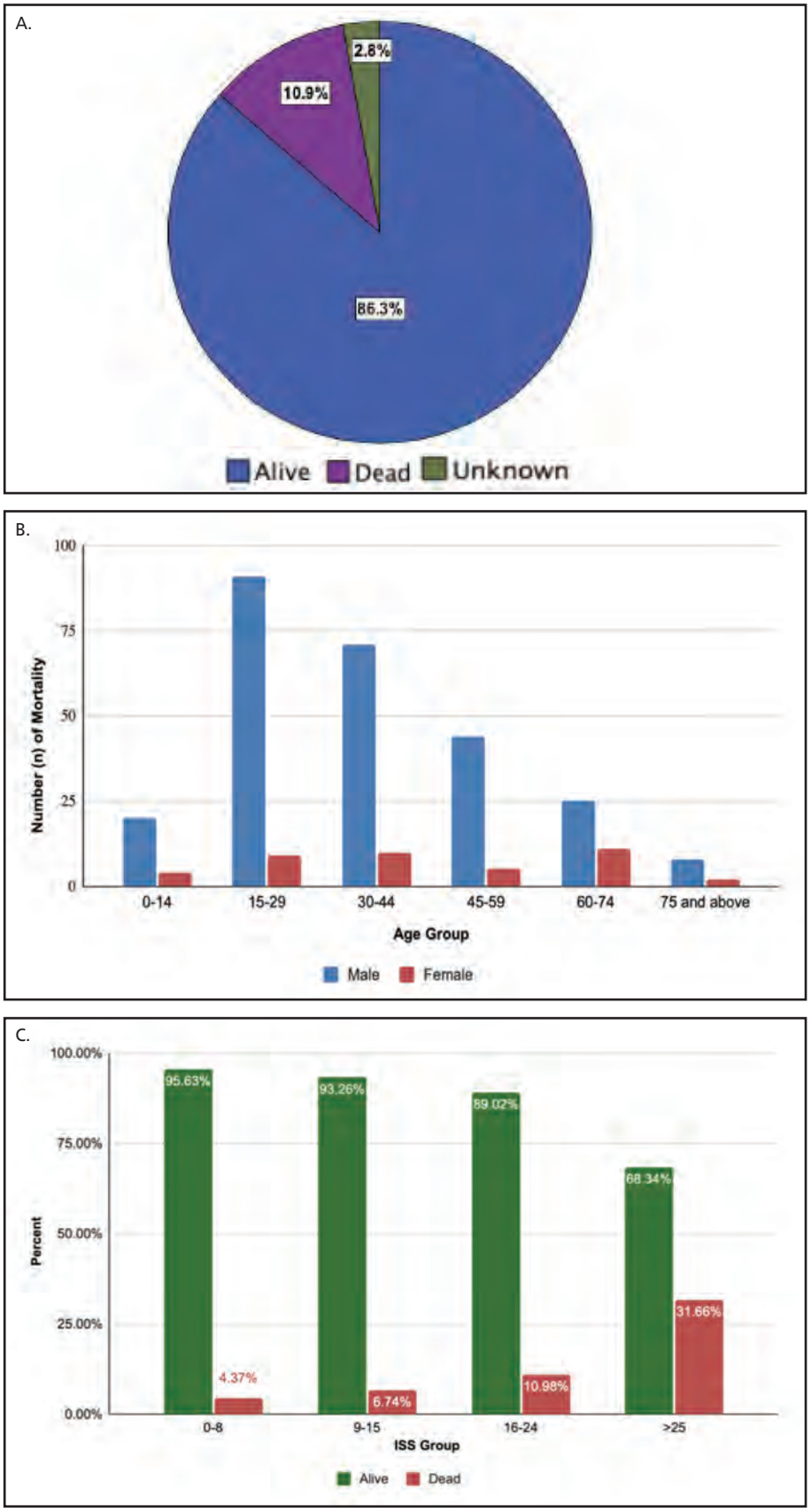

Fig. 4: A. Survival status B. Overall mortality by age group and gender (n=301) C. Outcome based on ISS

especially in hospitals without an Electronic Medical Record (EMR) system. To address these challenges, initiatives are underway to implement automated data extraction from EMR systems directly into the registry database. This integration aims to minimise manual data entry time for personnel while simultaneously improving data volume, completeness, and accuracy. Furthermore, hospitals currently utilising paper-based records, such as Hospital Kuala Lumpur are scheduled to transition to EMR systems in the near future, which will further streamline this process. Additionally, several errors within the MTR system were identified, requiring prompt rectification. A major error was the inability to download essential variables such as the types of vehicles involved in RTAs, safety devices used, and ICU length of stay. MTR administrators were notified of these issues during the study period.

Demographic data indicate that male adults aged 15-44 constitute the largest group involved in major trauma, with RTA identified as the predominant mechanism. This trend may be attributed to the high proportion of young males among road users and the heavy reliance on private vehicles for commuting, which is exacerbated by limited connectivity in the national public transportation system.[25,26] Interestingly, the second most common mechanism of injury, which was falls, mainly affected men in the middle-aged group instead of the elderly group, as it was among women. This may be due to middle-aged men being involved in high-risk occupations such as construction site work and engagement in outdoor activities. These evidences strongly indicates that young males should be the primary target population for injury prevention interventions.

PHC services in Malaysia are still in the developing stage, evidenced by the low percentage of major trauma patients arriving at the hospital by ambulance. Furthermore, only about one-third of them received on-scene assessments by ALS providers. This may have resulted in inappropriate prehospital triaging and treatment by unqualified providers, as evidenced by nearly half of the patients not being initially triaged to the EDCZ before being upgraded upon arrival in the ED. Ideally, all major trauma patients should receive an appropriate on-scene assessment by at least an ALS provider to improve outcomes.[27] At present, this is unachievable due to an insufficient number of ALS providers and ambulances within the MOH organisation to provide nationwide coverage. MOH relies heavily on support from non-governmental organisations such as St. John's Ambulance Service, staffed by personnel who are trained only to the Basic Life Support level. These shortcomings need to be addressed promptly to improve the quality of PHC services in Malaysia. Currently, the MTR dataset does not capture specialised prehospital certifications that emphasise trauma-specific modules, such as Prehospital Trauma Life Support or Prehospital Care Advanced Life Support. Incorporating this data would significantly enhance the registry's value by providing insights into the specialised training levels of responding personnel and their potential impact on patient outcomes. Additionally, the median time from emergency call to hospital arrival was 45 minutes. While this could be improved, it is comparable with other developing countries.[28]

A coordinated trauma reception is crucial to ensure the seamless delivery of care for major trauma patients upon their arrival at the hospital.[29] Ideally, major trauma patients should be resuscitated in a dedicated trauma bay in the ED to ensure the best outcome. MTR data showed that most of the major trauma patients were resuscitated at a shared resuscitation bay. This is because most hospitals in Malaysia lack a dedicated trauma bay due to various obstacles. Recognising its importance, several newly renovated EDs have incorporated dedicated trauma bays in their architectural plans. Although trauma team activation offers various advantages, it is not routinely practised in Malaysia due to limited human resources, ineffective interdisciplinary collaboration, and a lack of awareness of its importance.[30]

Studies have shown that mortality and morbidity significantly decrease when a major trauma patient is attended by a consultant from the outset.[31,32] However, this analysis revealed that only one-third of the patients were attended by a consultant upon arrival at the ED. Although this is significantly higher than what was reported in a previous local study, efforts must be made to ensure that all major trauma patients are attended by consultants in the near future.[23] This is feasible since all the hospitals that contribute data to MTR currently have resident emergency physicians. Their presence can enhance initial management, expedite decision-making, and facilitate various lifesaving interventions to be carried out safely in the ED.

Ultrasonography is now a crucial tool in Malaysian EDs, allowing for the rapid screening of internal injuries in trauma patients through the incorporation of eFAST into primary surveys. In terms of advanced imaging, selective CT scans were more commonly conducted than WBCT scans, due to the fact that only three public hospitals in Malaysia, Hospital Kuala Lumpur, Hospital Sungai Buloh, and Hospital Selayang, have a formally established WBCT protocol. The WBCT protocol for major trauma was only introduced in Malaysia four years ago, thus more time is necessary for its nationwide implementation. Research indicates that WBCT, when compared to selective CT, lowers overall mortality rates, decreases missed injury occurrences, shortens time to diagnosis, and reduces ED LOS.[33] WBCT also demonstrates high specificity (97.5-99.8%) and sensitivity (85.7-86.2%) in identifying injuries in the abdomen and pelvis.[34] The median time between arrival and the first CT scan in the ED was 95 minutes, significantly surpassing the 60-minute timeframe recommended by international guidelines.[34,35] One clear factor is the unequal distribution of patients needing CT scans and the limited availability of CT scan machines. Additionally, CT suites in Malaysia are often situated away from the ED, causing further delays. It is crucial to conduct a thorough assessment to pinpoint essential factors that could potentially reduce this time lag, ultimately speeding up clinical decision-making processes and reducing ED LOS.

Overall, only one-fifth of the major trauma patients required immediate emergency surgical intervention, such as exploratory laparotomy. This aligns with the current global trend favouring non-operative management (NOM) as the primary treatment strategy. This shift is driven by the introduction of damage control resuscitation, improved

access to advanced imaging, and the availability of IR services. NOM has proven highly successful in managing haemodynamically stable isolated liver and splenic injuries, regardless of their grade.[36-38] IR services are currently available in only a few hospitals in Malaysia which is the main reason for the very low number of patients who underwent IR interventions. On another note, it was noted that only 545 patients were admitted to the ICU, despite 791 patients being intubated. This indicates a shortage of ICU beds, resulting in suboptimal care that can adversely affect patient outcomes.

Most patients sustained head and neck injuries, followed by injuries to extremities and pelvic girdle. In terms of severity based on AIS, head, thoracic and lower extremity injuries recorded the highest severity. These injuries are often linked to a high number of RTAs, particularly among motorcyclists who are at greater risk of sustaining such injuries. Despite the failure to demonstrate that the motorcycle is the most common vehicle involved in RTAs in this study, this is a well-documented fact and has been published in multiple literatures.[23,39] Preventive measures to address this issue include creating separate lanes for motorcycles, implementing effective speed management systems, developing road safety education programs, adopting new technologies to enhance vehicle safety standards, and ensuring safer roads for all users.[39]

The outcome analysis revealed an in-hospital mortality rate of 10.9%, significantly lower than the previous local report but comparable to other developing countries.[23,40] However, this low mortality rate should be interpreted with caution, as nearly 60% of the patients in this study had an ISS of less than 16. The highest mortality rate was among patients involved in RTAs, aligning with Malaysian death statistics.[6] It was also identified that 70.1% of mortalities occurred in patients with an ISS >15. These indicate those who are severely injured due to RTAs should be the target group to reduce mortality. In the geriatric population, most deaths resulted from falls. While most prevention programs in Malaysia focus on reducing RTAs, fall prevention measures receive little emphasis. Given the rising geriatric population, fall prevention is a critical area needing urgent attention from relevant departments. It was observed that very few patients were transferred to rehabilitation centres upon discharge, highlighting a neglected area of care. Currently, there is only one public rehabilitation hospital in the country, indicating a need for greater focus on rehabilitation to reduce morbidity.

The primary limitation of this study was the sample size, with only 2,744 completed datasets suitable for final analysis. Several crucial variables within the completed datasets had significant missing information, such as HR and GCS. Additionally, we were also unable to retrieve variables such as types of vehicles, safety devices used, and length of ICU stay due to a system error. Furthermore, data accuracy might be less reliable than expected because the MTR is relatively new, having only been in operation for three years. There is a geographic imbalance in registry participation relative to state size. Specifically, the Klang Valley is over-represented despite its smaller geographic footprint, which may lead to the misconception that the current data is fully representative of the entire nation. However, as the MTR is currently in the recruitment phase, participation is expected to expand shortly to include university hospitals and other regions.

CONCLUSION

This epidemiological study highlights the significant burden of major trauma in Malaysia and provides critical insights into the current quality of trauma care nationwide. The findings serve as a platform to identify strengths and weaknesses, offering a roadmap for targeted enhancements in trauma management. Furthermore, these results provide a substantive basis for stakeholders to prioritise investment in trauma quality improvement programs. It is anticipated that this report will foster a greater commitment to data integrity among participating hospitals and catalyse the technical evolution of the registry itself. However, the sustainability of the registry and the feasibility of annual audits remain dependent on continued financial and technical support from the MOH. As shifting demographics and urbanisation continue to alter injury patterns, regular analysis of MTR data will be crucial for adapting trauma systems to meet evolving clinical demands.

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ETHICS STATEMENT

Informed consent was waived by the MREC, MOH due to the retrospective nature of the study. The study conformed to the principles outlined in the Declaration of Helsinki.

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DATA AVAILABILITY STATEMENT

Raw data are not attached. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Effect of multi-strain probiotics on enhancing apoptosis in lung cancer cells A549

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ABSTRACT

Introduction: Apoptosis is an important pathway for regulating cell proliferation and the occurrence of cancers such as lung cancer. The release of Caspase-9 and activation of Caspase-3 influence the process of apoptosis in lung cancer cells, making these proteins markers of apoptosis in lung cancer cells. Multi-strain probiotics show increased benefits due to the combined effects of different strains. The probiotic metabolites, such as short-chain fatty acids (SCFA), become important metabolites in lung immunity. This study aimed to examine the effectiveness of multi-strain probiotics in increasing apoptosis through increasing Caspase-3 and Caspase-9 expression in A549 cultures.

Material and Methods: The study was conducted in vitro using a cytotoxic assay to determine the IC_{50} value of multi-strain probiotics, followed by an In Cell Western assay to assess Caspase-3 and Caspase-9 expression.

Results: The cytotoxic assay IC_{50} result of the multi-strain probiotic was 58.952 ppm. Based on the result of the cytotoxic assay, the multi-strain probiotic in this study is not toxic to A549 lung cancer cells. In the Cell Western assay results, the multi-strain probiotic at concentrations of $2xIC_{50}$ and $0.5xIC_{50}$ showed the highest Caspase-3 and Caspase-9 expression, respectively, compared to the control group.

Conclusion: Multi-strain probiotics can stimulate the expression of Caspase-3 and Caspase-9 proteins in A549 lung cancer.

KEYWORDS:
Caspase-3; Caspase-9; lung cancer; multi-strain probiotics; apoptosis

INTRODUCTION

Lung cancer is one of the most fatal malignant cancers worldwide. According to GLOBOCAN 2020, it ranks second after breast cancer in terms of cancer incidence, with 2.2 million cases (11.4%). However, based on mortality rates, lung cancer ranks highest, causing 1.8 million deaths (18%), followed by colorectal cancer (9.4%) and liver cancer (8.3%).[1] Globally, Asia accounts for the largest proportion of lung cancer cases (58.2%), and Indonesia is one of the countries with the highest incidence, even ranking first in mortality.[2] Lung cancer risk factors fall into two main categories: genetic predisposition and environmental exposure. Environmental factors include smoking, chemical exposure, outdoor air pollution, exposure to metals, and ionising radiation. Smoking is the most dominant factor causing breast cancer and is responsible for 80% of cases in men and 50% in women.[3] Inhaled tobacco smoke contains approximately 4,000 chemical compounds, 69 of which are carcinogenic. Repeated exposure to tobacco and these carcinogenic agents can damage cells by affecting cell functions such as cell proliferation, apoptosis, and Deoxyribonucleic Acid (DNA) repair.[4]

Cellular disorders in lung cancer cause uncontrolled cell proliferation and impaired apoptosis. It begins with the release of cytochrome C due to changes in membrane permeability, and then activates apoptotic protease-activating factor-1 (Apaf-1). Apaf-1 will combine with proCaspase-9 to form an apoptosis complex that activates Caspase-9.[5] Caspase-9 will activate the Caspase-3 protein, and then the cytoplasmic endonuclease will be activated. This mechanism plays a role in degrading DNA chromosomes and the cytoskeleton. Then, nuclear fragmentation will form apoptotic bodies, which are phagocytosed by phagocytic cells.[6] However, in many cancers, such as lung, breast, prostate, colon, and colorectal cancer, apoptosis is suppressed due to overexpression of anti-apoptotic proteins like B-cell lymphoma 2 (Bcl-2) and downregulation of pro-apoptotic proteins like Bcl-2-associated protein X (BAX). Thus, it hinders Caspase activation and promotes resistance to therapy.[7] Lung cancer treatment involves several treatment modalities, including surgery, radiotherapy, systemic therapy (chemotherapy, immunotherapy, and targeted agents), radiological interventions, and palliative care.8 While chemotherapy is widely used, it often causes collateral damage to healthy cells and faces challenges due to cancer resistance, often caused by dysregulated apoptotic mechanisms.[9] Unfortunately, resistance to chemotherapy is an obstacle to treating lung cancer effectively.[8]

Probiotics have gained attention as potential adjuvant therapies in cancer management due to their

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antiproliferative and pro-apoptotic effects. Probiotics can downregulate nuclear factor-kappa B (NF-κB), reducing Bcl-2 expression and promoting apoptosis.[10] Many probiotics have shown benefits, including *Lactobacillus* spp., which are found in the gastrointestinal tract, vagina, oral cavity, respiratory tract, and skin. The use of probiotic *Lactobacillus* has been widely studied for its involvement in the treatment of lung cancer.[11-15] A single-strain study of *L. rhamnosus* administration to mice showed that the probiotic can inhibit B16 melanoma metastasis in the lungs.[12] In vitro test of L. casei administration showed a significant inhibitory effect on the proliferation of A549 lung cancer cells.[13] In other studies related to the administration of *L. casei*, it can increase antitumor activity against lung carcinoma in mice.[14] In addition, administration of *L. casei* reduces the side effects of chemotherapy so that it can improve the prognosis of lung cancer patients.[15] This suggests that some *Lactobacillus* may have the potential to be effective adjuvants for treating lung cancer. In recent years, many studies have reported the relationship between the gut and lungs, which is described as the gut-lung axis.[16-18] Some potential mechanisms for Lactobacillus to reach the lungs: *Lactobacillus* or its components and metabolites, such as short-chain fatty acids (SCFAs), which are in the intestinal lumen and then taken up by intestinal epithelial cells, enter the lungs through circulation, or by *Lactobacillus* or its components from the intestinal lumen reaching the lungs directly through micro breathing or oesophageal reflux.[19]

The use of multi-strains has its advantages because the characteristics of the different strains can increase colonization, so the chances of survival of the probiotic strain increase.[20] The use of multi-strain probiotics may show increased benefits from the preparation due to the combined effects of different strains in one preparation compared to a single strain. Having multiple strains can help maximize the scope of benefits and provide complementary benefits to each other.[21] Current research related to the use of multi-strain probiotics in lung cancer is still limited, so further in vitro research is needed to determine the anticancer activity of multi-strain probiotics against A549 lung cancer cells using the Resazurin assay method with PrestoBlue reagent to obtain the IC_{50} value. After obtaining the results of the cytotoxic test in the form of an IC_{50} value, it was continued with the In Cell Western Assay (ICW) test to see the effect of administering multi-strain probiotics in increasing apoptosis in A549 lung cancer cell cultures through the expression of Caspase-3 and Caspase-9.

MATERIALS AND METHODS

Cell Line A549 Culture

A549 cells were thawed in a 37°C water bath until fully melted. The cells were resuspended in Roswell Park Memorial Institute (RPMI) media, then centrifuged at 3000 rpm for 5 minutes. The pellet was resuspended and cultured in a 3 cm petri dish with 2.5 ml of media, incubated for 24 hours, and monitored for >80% confluence. Once confluence exceeded 80%, the media was removed, the dish was rinsed twice with PBS, and 0.2 ml of trypsin was added, followed by a 5-minute incubation. After adding 1.3 ml of media, the cells were divided into three microtubes and centrifuged. The pellet from the first tube was cultured in a 10 cm petri dish with 10 ml RPMI media for further analysis, while pellets from the second and third tubes were stored in cryotubes with media and 10% Dimethyl Sulfoxide (DMSO) as stock.

Cytotoxic Assay

Toxicity testing was carried out using the Resazurine method using Presto BlueTM reagent.[22] A549 cells that have been incubated in the reculture process and confluence >80% indicate that the cells are ready for seeding. The media in the reculture petri dish is removed, rinsed 3 times using PBS, and 1 ml of trypsin is added. Incubate for 5 minutes to detach the cells, followed by the addition of 1 ml of media. After homogenization, the cell suspension was centrifuged at 3000 rpm for 5 minutes. The pellet was resuspended with 1 ml of media, then 10 µl of the suspension was mixed with 10 µl of trypan blue. A 10 µl aliquot of this mixture was used for cell counting with a hemacytometer. Cell calculation uses the following formula [1]:

$$\text{Counted cell count (cell/ml)} = \frac{(\text{number of living cells})}{4} \times \text{dilution factor} \times 10.000 \quad [1]$$

Planting cells in a 96-well plate has a target of 75.000 cells/well, so the volume of cells that can be transferred can be calculated using the following formula [2]:

$$\text{Volume of cells transferred} = \frac{\text{Total number of cells required}}{\text{Counted cell count)}} \quad [2]$$

Cells that have been planted in 96-well plates will be incubated and their confluence observed before being given the treatment. Treatment was carried out by adding blanks, media, Doxorubicin (positive control), solvent control (Mili-Q), and samples with various concentrations. The tests were performed in triplicate. Incubation was carried out for 48 hours. Presto blue was added with a 1:9 ratio of presto blue and media. The addition of presto blue to each well is 100µl, then incubated for 2 hours. The plate will be read at a wavelength of 570 and 600nm to measure absorbance, which will then be converted into a percentage of viability using a multimode reader Tecan 200M pro.

IC50 calculation from the experimental results obtained from absorbance from 3 types of controls and test compounds, including cell control (culture media + cells), solvent control (cell culture media + milli-Q water), positive control (Doxorubicin), and test compound (culture media + cells + test compound). The IC_{50} calculation step using the percentage of cell viability uses the following formula [3]:[23]

$$\%\ \text{Living Cell} = \frac{(\text{Absorbance of Treatment-Absorbance of Control Media})}{(\text{Absorbance of Cell Control-Absorbance of Control Media})} \times 100\% \quad [3]$$

In Cell Western Assay

A549 cells with a confluent level of >80% were counted using a hemacytometer. Cells were seeded and treated with various concentrations of the samples and incubated for 48 hours. The tests were performed in triplicate. Reagents in the form of secondary antibodies, Cell-Tag 700, washing solution

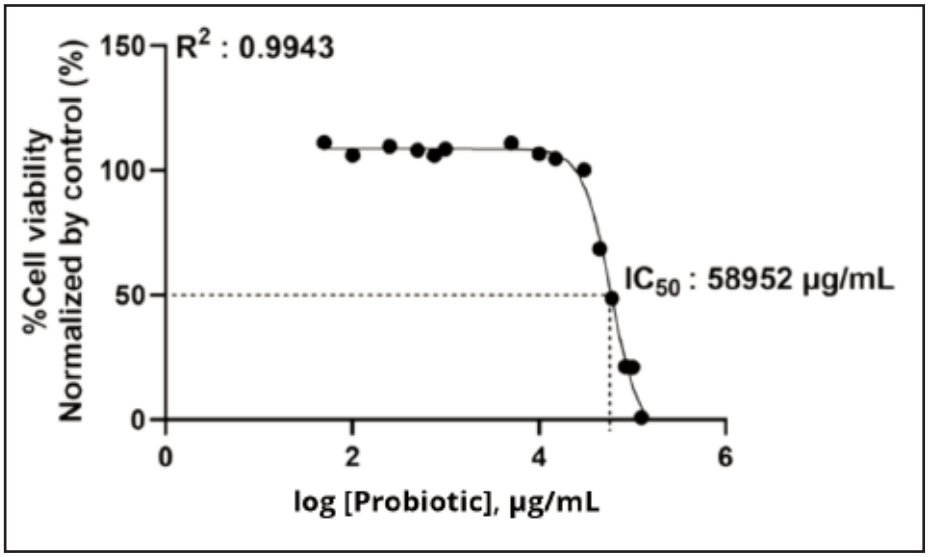

Fig. 1: Cytotoxic test result curve of multi-strain probiotic on A549 lung cancer cells.

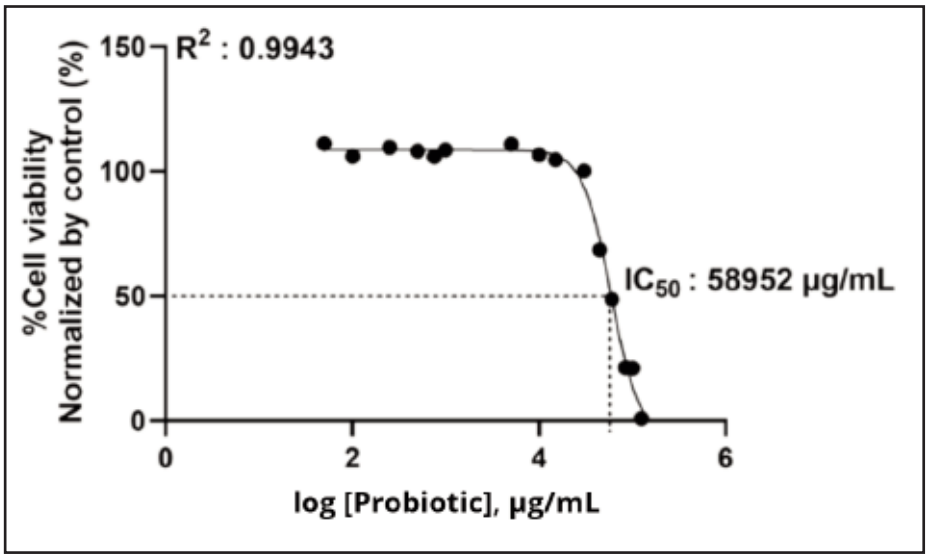

Fig. 1: Caspase-3 fluorescence results of multi-strain probiotic.

*A1-B1: Negative control background; C1-D1: Positive control background; A2-B2: Negative control; C2-D2: Positive control; A3-D3: Multi-strain Probiotic Background ½, 1, 1½, 2 x IC_{50}; A4-D4: Multi-strain Probiotic ½, 1, 1½, 2 x IC_{50}; A5-D5: Multi-strain Probiotic ½, 1, 1½, 2 x IC_{50}.

(Tween-20 + Tris buffer), fixation solution (37% formalin + Tris buffer), and permeabilization solution (10% Triton X-100 + Tris buffer) were prepared. A total of 150 µL of fixation solution was added to a 96-well microplate and incubated for 20 minutes on a rocker shaker, then the fixation solution was discarded. 150µL of permeabilization solution was added and incubated for 20 minutes, then the solution was discarded. 150µL of blocking solution was added, incubated for 30 minutes, and then the solution was discarded. A 50µL diluent solution was added to the background well, while 50µL of primary antibody was added to all other wells. The wells were then incubated overnight at 2–8°C. After incubation, the primary antibody solution was discarded, and 150µL of wash solution was added and incubated for 5 minutes; it was then discarded. This washing step was repeated four times. A 50µL secondary antibody without Cell-Tag 700 was added to the background well. In comparison, 50µL of secondary antibody with Cell-Tag 700 was added to the remaining wells and incubated for 1 hour, then discarded. Four more washes were performed with the wash solution. The 96-well microplate was then read using Odyssey® XF.

Statistical Analysis

The results obtained in this study were the percentage of living cells and the expression of Caspase-3 and Caspase-9. The living cell data obtained were analysed using statistical methods with the GraphPad Prism 9 program. The results of the analysis obtained with this program were in the form of

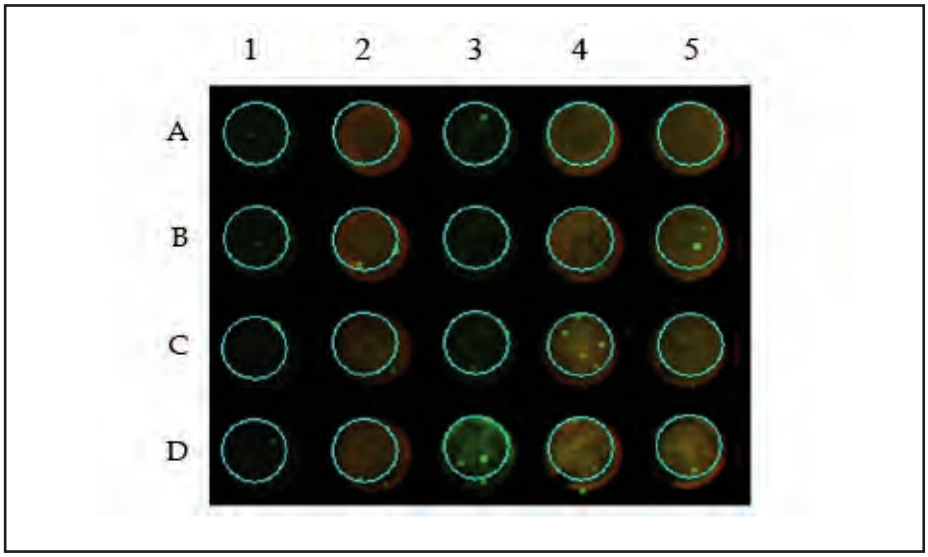

Fig. 3: Caspase-9 fluorescence results of multi-strain probiotic.

*A1-B1: Negative control background; C1-D1: Positive control background; A2-B2: Negative control; C2-D2: Positive control; A3-D3: Multi-strain Probiotic Background ½, 1, 1½, 2 x IC_{50}; A4-D4: Multi-strain Probiotic ½, 1, 1½, 2 x IC_{50}; A5-D5: Multi-strain Probiotic ½, 1, 1½, 2 x IC_{50}.

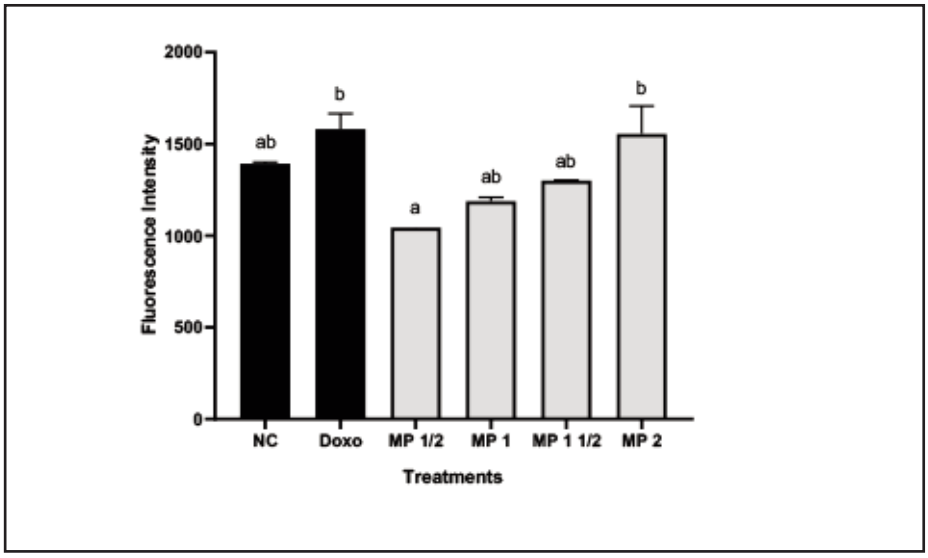

Fig. 4: Caspase-3 protein expression in multi-strain probiotic

(NC: Negative Control; Doxo: Doxorubicin; MP1/2: Multi-strain Probiotic ½ x IC_{50}; MP1: Multi-strain Probiotic 1 x IC_{50}; MP1,5: Multi-strain Probiotic 1,5 x IC_{50}; MP2: Multi-strain Probiotic 2 x IC_{50})
*The result was shown as mean ± SEM. Tukey's HSD post hoc test is used to produce statistical differences. The various letters (a,ab,b) demonstrate a significant difference between various treatments toward A549 lung cancer cell line.

IC_{50}. The results of observations of Caspase-3 and Caspase-9 protein expression were analysed using SPSS Statistics version 20.0. After a normality test was performed, normal data were analysed with analysis of variance followed by Tukey's HSD post hoc test, with a significance threshold of $p \leq 0.05$.

RESULTS

Cytotoxic Assay

Toxicity testing was carried out using the Resazurine method, which aims to determine the toxic effects of probiotics and measure the concentration of these probiotics on A549 lung cancer cells. The concentration tested based on the literature is 50, 100, 250, 500, 750, 1.000, 5.000, 10.000, 15.000, 30.000, 45.000, 60.000, 85.000, 100.000, 125.000, 150.000 ppm. The use of PrestoBlue reagent in this method will result in a colour change from the blue resazurin compound to the pink resazurin compound due to the reduction by enzymes in

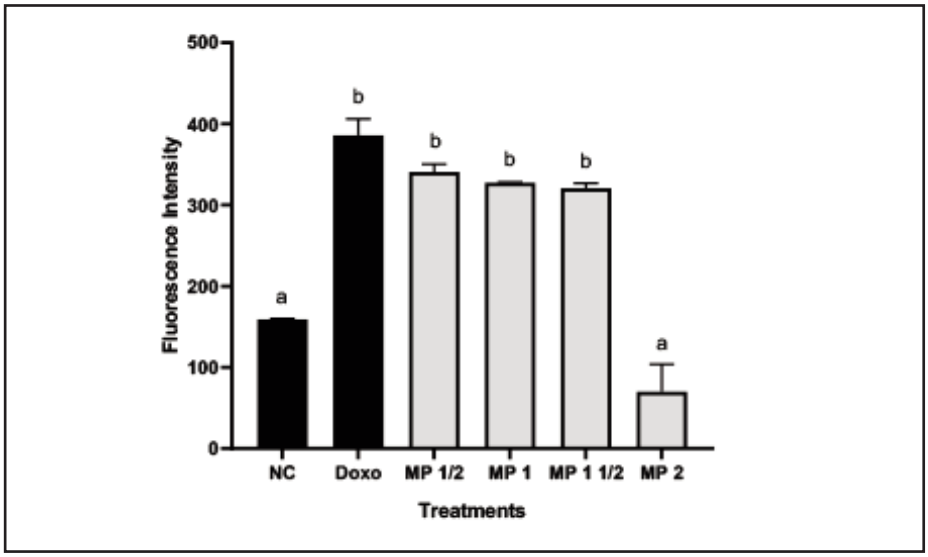

Fig. 5: Caspase-9 protein expression in multi-strain probiotic

(NC: Negative Control; Doxo: Doxorubicin; MP1/2: Multi-strain Probiotic ½ x IC50; MP1: Multi-strain Probiotic 1 x IC50; MP1,5: Multi-strain Probiotic 1,5 x IC50; MP2: Multi-strain Probiotic 2 x IC50)
*The result was shown as mean ± SEM. Tukey's HSD post hoc test is used to produce statistical differences. The various letters (a,b) demonstrate a significant difference between various treatments toward A549 lung cancer cell line.

the mitochondria. Then the absorbance will be measured at a wavelength of 570 and 600nm with the Multimode Microplate Reader Tecan Infinite m200 Pro. Figure 1 shows the cytotoxic test curve of multi-strain probiotics on A549 lung cancer cells.

In Cell Western Assay
The Caspase-3 fluorescence results of the multi-strain probiotic can be seen in Figure 2. The red colour is the result of a wavelength of 700 nm, which aims to determine the number of cells, while the green colour indicates the expression of Caspase-3 protein (primary antibody) from a wavelength reading of 800 nm.

The fluorescence results of Caspase-9 from the multi-strain probiotic can be seen in Figure 3. The red colour is the fluorescence result from a wavelength of 700 nm, which aims to determine the number of cells, while the green colour indicates the expression of Caspase-9 protein (primary antibody) from a wavelength of 800 nm. Figure 4 shows the graph of Caspase-3 expression in multi-strain probiotics. Meanwhile, Figure 5 shows the graph of Caspase-9 expression in multi-strain probiotics.

DISCUSSION

Multi-strain probiotics are a type of probiotic that contains more than one strain of bacteria originating from the same species, or from different species, such as containing fungi species (*Saccharomyces* species).[24] The use of multi-strain probiotics can show better inhibitory effects on enteropathogens and increase the benefits of the preparation due to the combined effects of different strains in one preparation compared to single strains.[25] Therefore, testing was conducted using probiotic finished products containing multi-strain probiotics, such as *L. bulgaricus, L. rhamnosus, L. fermentum, L. casei, L. plantarum*, and *Rhodopseudomonas palustris*. Initial testing was conducted by conducting a toxicity test using the Resazurin method to determine the magnitude of Inhibitory Concentrations 50% (IC_{50}) against A549 lung cancer cells.

Probiotic toxicity is obtained due to the activity of postbiotic metabolites contained in probiotics. The term postbiotic refers to micro- and macromolecular complexes, such as inactivated microbial cells, cell fractions such as muropeptides, teichoic acids, endo and exopolysaccharides, and proteins on the surface layer, or cell metabolites such as SCFA, organic acids, bacteriocins, and enzymes formed due to the fermentation process that occurs in probiotics.[26] Therefore, initial testing of the toxicity of the multi-strain probiotics used may reflect the activity of postbiotic metabolites such as SCFAs present in the multi-strain product.

Several studies that have previously obtained IC_{50} values are studies using Lactobacillus lactis KC24 obtained from kimchi isolation in SK-MES-1 cells with a concentration of 106 CFU/well capable of inhibiting proliferation by 86.53%, and *Lactococcus lactis* NK34 in SK-MES-1 cells with a concentration of 106 CFU/well capable of inhibiting proliferation by 96%.[27,28] Based on the cytotoxicity test result curves in Figure 1, the IC_{50} value of the multi-strain probiotic on A549 lung cancer cells is 58.952 ppm. The higher the IC_{50} value, the higher the concentration required to inhibit cancer cells by 50% is also higher. Referring to the classification of the cytotoxic strength of compounds, compounds with IC_{50} <100ppm are categorized as potentially cytotoxic, compounds with IC_{50} between 100-1000ppm are categorized as moderately cytotoxic, and compounds with IC_{50}

>1000ppm are categorized as non-toxic, so the multi-strain probiotic product tested is included in the non-toxic category.[27]

The IC_{50} results of multi-strain probiotic products in testing on A549 lung cancer cells can be influenced by several factors. Interactions between probiotic strains contained in multi-strain products can affect each other's effectiveness.[28] Differences in strains can provide different mechanisms of action and provide a greater scope of effects.[29] Unfortunately, this can also cause antagonistic intra-strain inhibition of different probiotic strains.[30] Research using multi-strain probiotics containing *L. plantarum, L. rhamnosus, L. acidophilus, Enterococcus faecium* showed that *L. plantarum* was the strongest strain in inhibiting *L. rhamnosus*, and *Vice versa*, while *L. plantarum* and *L. rhamnosus* were the strongest strains in inhibiting *L. acidophilus* and *Enterococcus faecium* in the product.[31] Other studies were conducted by analyzing single and multi-strain probiotics using 14 different strains to determine the inhibitory effects between strains using the cross-streak assay method and agar spot test.[30] The strains used were *L. acidophilus, L. delbrueckii subsp bulgaricus, L. casei, L. plantarum, L. rhamnosus, L. salivarius ssp Salivarius, L. fermentum, L. helveticus, Lactococcus lactis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum,* and *Streptococcus thermophilus*. The results obtained were from the *Lactobacillus* group, *L. casei* could inhibit *L. plantarum* weakly, inhibit *L. rhamnosus* moderately, and inhibit *L. fermentum* weakly. However, when compared with other groups, *Lactobacillus* is a probiotic with the strongest strain to inhibit other bacterial groups ($p<0.001$).[30]

In the probiotic product, there are five types of *Lactobacillus* strains mixed with *Rhodopseudomonas palustris* where, when compared to previous studies, *L. plantarum* will have the most dominant effect to inhibit other strains. It can be concluded that the type of strain used in a multi-strain probiotic product greatly determines whether the product is able to increase the effectiveness of each other between strains or can actually reduce the activity of other strains, as in previous studies.[32] The interaction between strains contained in this multi-strain product will affect postbiotic metabolites such as SCFA, which are expected to increase when strains are combined in multi-strain products.

In addition to strain-specific activity, the effectiveness of SCFAs as bioactive metabolites is influenced by several factors, including osmotic pressure, environmental pH, nutrient availability, and energy sources required for SCFA synthesis. In this study, the multi-strain probiotic formulation had a pH of 3.10, while the optimal pH range for SCFA production is 5.5–6.0. An environment that is too acidic ($pH<5.5$) can inhibit acidogenic activity. As a result, SCFA production is likely to be disrupted, so the effectiveness of probiotics in inducing apoptosis may not be optimal. Under physiological conditions, normal cells maintain a pH range of 7.35-7.45, while cancer cells exhibit a more acidic pH between 6.3 and 7.0 due to altered metabolic activity. Exposure of multi-strain probiotics to A549 lung cancer cells with low pH may further acidify the intracellular environment, potentially disrupting SCFA-mediated apoptotic signals and allowing cancer cells to survive.

SCFA itself is an intermediate compound synthesized in the anaerobic digestion process from substrates such as polysaccharides, proteins, and lipids. These substrates will be hydrolyzed first before entering several pathways for the formation of SCFA.[33] Pyruvate will be produced through the glycolysis pathway, and propionate will be produced through the succinate or propanediol pathway. Butyrate will be produced through the activity of the butyrate kinase enzyme. Acetate will be produced from the activity of the acetate CoA transferase enzyme.[34,35] The anaerobic digestion process from hydrolysis to various fermentation pathways to obtain these SCFAs cannot be observed in this study, because the exposure of multi-strain probiotics directly to A549 lung cancer cells occurs without any digestion process.

Further testing was conducted to observe the expression of Caspase-3 and Caspase-9 proteins as apoptosis markers after exposure to a multi-strain probiotic in A549 lung cancer cells. Apoptosis is a form of non-inflammatory programmed cell death mediated by Caspase activation that can occur through intrinsic or extrinsic pathways.[36] The intrinsic pathway is a pathway that is activated due to mitochondrial damage, where cytochrome c will be released into the cytoplasm along with Apaf-1, which will then form an apoptosome, where this apoptosome will activate Caspase-9. Caspase-9, which is an initiator Caspase, will then activate Caspase-3 as an executor Caspase in the apoptosis process.[37]

In this study, tests were conducted to see Caspase expression at concentration ranges of 0.5x IC_{50}, 1xIC_{50}, 1.5xIC_{50}, and 2xIC_{50}. The Caspase-3 expression of the multi-strain probiotic showed a significant difference ($p\leq0.05$). The multi-strain probiotic at a concentration of 2xIC_{50} showed higher Caspase-3 expression compared to the other group. The multi-strain probiotic at a concentration of 0,5xIC_{50} gave the highest Caspase-9 expression. The expression of Caspase-3 and Caspase-9 is influenced by the activity of SCFAs exposed by the administration of a multi-strain probiotic. In previous studies, research on SCFA type sodium butyrate with a concentration of 5mM was able to reduce proliferation and migration of A549 lung cancer cells and could increase the expression of miR-3955.[38] As for propionate, it was found that at a concentration of 10mM of sodium propionate it was able to reduce proliferation and increase cell cycle arrest and could increase apoptosis in H1299 and H1703 human non-small cell lung carcinoma cells.[39]

In lung cancer, SCFA type butyrate can accumulate as a histone deacetylase (HDAC) inhibitor in the nucleus, where HDAC is an enzyme that plays a role in tumour cell expression.[37] Accumulation of HDAC inhibitor from butyrate is then able to increase inhibition of lung cancer cell expression and increase the apoptosis process by increasing proapoptotic proteins such as BAX and BCL-2 homologous antagonist/killer (BAK) or through a pathway of decreasing the expression of anti-apoptotic proteins such as Bcl-2.[40] In addition to butyrate, SCFA type propionate can activate cell apoptosis and the cell cycle by decreasing Survivin expression and increasing p21 expression. Survivin is an antiapoptotic protein whose expression increases in several types of cancer,

one of which is lung cancer. With a decrease in Survivin expression, there will be induction of BCL-2–associated death promoter (BAD) and BAX expression, where there will be induction of cells entering the G2/M arrest phase.[39]

It has been explained previously that due to the absence of a digestion process because A549 lung cancer cells were exposed to probiotics directly, it can result in the anaerobic digestion process may not be optimal to obtain SCFA, which can affect the amount of SCFA obtained in the research samples used. In this study, quantitative measurements were also not carried out on the amount of SCFA, such as butyrate or pyruvate concentrations, which are suspected of affecting A549 lung cancer cells.

In previous studies, the use of cell-free supernatant in lung cancer research was carried out on the testing of *Faecalibacterium prausnitzii* cell-free supernatant form on A549 lung cancer cells by measuring anti-inflammatory cytokines such as Interleukin (IL)-10, Tumour Growth Factor (TGF)-β2, and IL-1Ra.[40] The results of this study showed that multi-strain probiotics were able to dysregulate the expression of several cytokines. This is as seen in the results of Caspase-3 and Caspase-9 expression in this study, where Caspase-3 and Caspase-9 can still be expressed. Despite the suboptimal formation of SCFAs and the non-toxic nature of multi-strain probiotics, as demonstrated by cytotoxicity assay, this study demonstrated that the probiotic formulation effectively stimulated apoptosis in A549 lung cancer cells. Specifically, Caspase-3 expression was significantly increased at a concentration of 2×IC_{50}, while Caspase-9 expression peaked at 0.5×IC_{50}.

CONCLUSION

A multi-strain probiotic is included in the non-toxic category, with IC50 values in cytotoxic tests conducted on A549 lung cancer cells of 58.952ppm. The use of a multi-strain probiotic at a concentration of 2xIC_{50} can stimulate the expression of Caspase-3. The use of multi-strain probiotics at concentrations of 0.5xIC_{50} can stimulate the expression of Caspase-9 in A549 lung cancer. Thus, multi-strain probiotics can activate major apoptotic pathways without causing cytotoxic effects, indicating their potential as a safe and effective adjuvant therapy for the treatment of lung cancer.

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AUTHOR CONTRIBUTIONS

MEG contributed to the conception and design of the study, definition of intellectual content, data analysis, manuscript editing, and manuscript review. RL contributed to liter ature research, conducted experimental studies, performed data acquisition, and participated in manuscript preparation and review. GRG was responsible for literature research, experimental studies, data acquisition, statistical analysis, manuscript preparation, and review. IGYD conducted experimental studies and statistical analysis, and contributed to manuscript editing and review. AK was involved in the conception and design of the study, definition of intellectual content, data analysis, manuscript editing, and manuscript review.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest regarding the data presented in this manuscript.

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A descriptive evaluation of referral patterns and patient flow from Primary Health Facilities to the Emergency Department Hospital Sungai Buloh

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ABSTRACT

Introduction: Referrals from Primary Health Facilities (PHF) to hospitals occur due to clinical needs for speciality care in managing the presenting illness, social factors such as poor compliance or lack of family support, and are requested by patients. The journey for any patients transferred from PHF to hospitals has three major components, which are (a) the PHF intervention and activation of ambulances; (b) the Prehospital Care Services (EMS) deployment, care of the patient and transportation to the hospital; and (c) the process of review or admission at the destination hospital. We detail the journey, processing time, and outcomes of patients referred from PHFs via EMS to a tertiary referral hospital in Selangor, Malaysia.

Materials and Methods: This is a retrospective study analysing data from 980 referred patients from PHFs transported by Klang Valley Ambulance Service (KVAS) to Hospital Sungai Buloh between 1st January 2023 and 30th June 2023. Data collected includes PHF classification, KVAS activation details, patient demographics, Emergency Department length of stay (EDLOS), and the patient's outcome in the ED. Patient's outcome in ED is categorised as (a) admitted; (b) discharged; or (c) discharged against medical advice (DAMA).

Results: Out of the 980 referred patients, 83.3% were triaged as Priority 1 by PHFs. The majority were males (56.8%), with a mean age of 28 years. The median waiting time for ambulance arrival was 54-58 minutes. The percentage of referred patients who were admitted to the ward was 65.8%. The median EDLOS was 540 minutes (9 hours), with discharged patients having a shorter median EDLOS of 321 minutes (approximately 5 hours). The median total patient waiting time from PHF to final disposition was 605 minutes (10 hours) for admitted patients and 382 minutes (6 hours) for discharged patients.

Conclusion: A significant proportion of referred patients experienced prolonged EDLOS, whereas only 22.4% of referred patients were discharged within eight hours. Average EDLOS of 12 hours suggests the need for a "Fast-Track Referral System" to improve efficiency and reduce unnecessary gatekeeping processes.

KEYWORDS:
Emergency Department; Emergency Medical Services; Interfacility referral; Primary Health Care; Length of stay

INTRODUCTION

Public Primary Health Facilities (PHF) referral process involves the transfer of patients from one facility to another to meet the increased demands for services.1 This can involve transfers either between hospitals or transfers from a clinic to a hospital to provide the clinical needs of patients. The reasons for transfer from PHF to hospitals may include (a) the need for specialty expertise in managing the presenting illness, (b) social factors such as poor compliance or lack of family support; (c) request by patients to be admitted.[2] The Ministry of Health Malaysia (MOH Malaysia) defines basis for interfacility transfers into four categories or reasoning: (a) step-up care to a centre with better expertise or facilities to treat the patient; (b) same level care for logistics reasoning in the primary facility; (c) step-down care for continuation of treatment after stabilisation; and (d) at the request of patient or family.[3] The journey for any patients transferred from PHF to hospitals has three major component which are assessment and intervention by PHF, activation and transportation by EMS and the process of review or admission at the destination hospital. The interaction between the three components affects the patient in terms of the cost of transportation for family members or caregivers and additional waiting time at the receiving facility, especially in the Emergency Department (ED).[1]

The usual disposition of ED patients after assessment can be divided into four categories: (a) discharged without the need for observation; (b) observation for a short duration before discharge; (c) admission for inpatient care; and (d) died in the

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ED. The ED in Malaysia has a policy that states all patients are to be admitted to inpatient services within an 8-hour timeline from consultation and care.[4] However, in the current burden of ED access block, it is challenging to meet the 8-hour timeline. The ED Observation services are not considered as inpatient services based on the national ED policy.[4] While waiting for an inpatient bed, patients requiring admission may have completed their treatment and been discharged from the ED due to their prolonged length of stay. The ED length of stay (EDLOS) is defined as the time interval between a patient's arrival at the ED and the time the patient physically leaves the ED.[5] The EDLOS is an accepted marker for clinical interventions, system organisation, and an indicator of ED overcrowding.[6]

ED has yet to have a policy and pathway that separates referred patients from walk-in patients to the department. Thus, there is a need to have a gatekeeper for the referral system. Without the barrier of a gatekeeper, the problem of ED access block may be compounded further.[7] Family Medicine Specialists (FMS) are gatekeepers to ensure appropriate utilisation of the referral system.[8] The elements considered by FMS for referrals include the coordination of care, control of referral, and financial and social factors on a case-by-case basis.[8] The role of FMS as gatekeeper has been studied from the perspective of appropriateness of referral and of admission. Ang et al., classified referrals as appropriate or inappropriate based on the patient's condition, the reason for referral and the management capacity of the referring clinic.[9] Study by Chan S., classifies referral and its eventual admission as appropriate or inappropriate based on benefit and services received by the patient.[2] A referral with eventual admission is deemed inappropriate when patients do not derive any significant benefit or when no active services are provided, and where the best care can be rendered in a less costly manner at a lower level of care.[2] There has never been a study that reviews PHF referrals from the perspective of the patient's journey and length of stay within the ED.

This study aims to describe the journey, processing time and outcome for patients referred from PHF transported using EMS to a tertiary referral hospital in Selangor. Through this observational study, we hope to assist health system managers on the policy of care pathways in hospitals for patients who have been assessed and referred from PHF. By understanding the demand, processes, and flow of patients, policy makers would be able to identify potential areas of system improvement.

MATERIALS AND METHODS

This is a retrospective descriptive study involving referred patients from PHF to ED Hospital Sungai Buloh from 1st January to 30th June 2023. The institutional approval reference is NMRR ID-24-01225-Q75. The study included data of all patients referred from PHF to Hospital Sg Buloh Specialty Services via the ED. EMS in Sg Buloh utilises the Klang Valley Ambulance Service (KVAS). Only patients transported using KVAS are included in the study. Pregnant mothers referred for Obstetrics Services, or patients for direct admission, or any patients that are referred out to another facility are excluded from the study. Such patients have specific pathways that bypass the general patient flow in the ED. Our study is aimed at describing the patient flow processes with key time matrices in obtaining Speciality care from PHF.

PHF data collected encompasses patients' triage classification during KVAS activation and basic emergency intervention provided to patients by the PHF prior to KVAS arrival. The basic emergency interventions provided are categorised as oxygen or intravenous fluid administration or none. Fluid administration is subclassified into either bolus or maintenance. KVAS established an ambulance activation system using an electronic form that is completed by PHF. The form collects the patients': (a) demographic information, (b) basic emergency intervention provided by PHF, (c) triage categorisation of patients by PHF, and (d) referral communication by PHF to the destination hospital. KVAS and PHF utilise a two-tier ambulance triaging system. The two-tier triage system classifies patients as requiring Priority 1 or Non-priority 1 response. Priority-1 triage category is assigned by PHF based on patients' physiological parameters, clinical syndrome, together with the National Guidelines for Primary Care ambulance service.[10] The Priority 1 classification used in the national guidelines is adapted from the Medical Priority Dispatch System (MPDS, Priority Dispatch Corporation) version 10.

The patients' demographic data analysed are gender and age. KVAS data of the patient's transport time were also utilised for analysis. Our team reviewed ED and Bed Management Unit data for EDLOS and the outcome for patients in the ED. Patient's final outcomes are divided into three categories: (a) admitted; (b) discharged; or (c) discharged against medical advice (DAMA). We define admission as any in-patient bed is made available for the patient and the patient being successfully transferred to the ward. We define discharge as any patient discharged from the ED either by the ED team after a period of observation, or by the Speciality team upon completion of treatment while waiting for an inpatient bed. Patients' age, and EMS transport times are summarised using mean, standard deviation and median quartiles. Categorical data are summarised using frequency, percentages and statistics are analysed using the Pearson Chi-Square method. Incidence rates and outcomes are tabulated in frequencies and percentages according to PHF triage categories of either Priority 1 or Non-priority 1 for comparison. EDLOS are tabulated as admission or discharged categories for comparison. Data analysis utilises SPSS Statistical software version 29.

RESULTS

Between 1st January and 30th June 2023, a total of 980 referred patients from PHF to Hospital Sungai Buloh were included in this study for analysis. Table I describes the patient demography. A total of 557 (56.8%) of the patients are male. The mean age of patients is 28 years (SD ±23), where 515 (52.6%) of them were adults. Overall, 816 (83.3%) patients were triaged by PHF as Priority 1 during EMS activation. An outcome of 645 (65.8%) referred patients were

Table I: Referred patients' demography and the final outcome at Emergency Department

	ALL N=980 n (%)	PRIORITY 1 N=816 n (%)	NON-PRIORITY 1 N=164 n (%)	p-value
Gender				
Male	557 (56.8)	472 (57.8)	85 (51.8)	0.156[a]
Female	423 (43.2)	344 (42.2)	79 (48.2)	
Age				
Mean	28	28	26	
Median	25	25	26	
Std Deviation	±23	±22.8	±21.2	
IQR 25	6	6	6	
IQR 75	45	45	43	
Category of age				
Paediatric	337 (34.4)	283 (34.7)	54 (32.9)	0.398[a]
Adolescent	61 (6.2)	47 (5.8)	14 (8.5)	
Adult	515 (52.6)	427 (52.3)	88 (53.7)	
Geriatric	67 (6.8)	59 (7.2)	8 (4.9)	
Outcome of Patient in Emergency Department				
Admit	645 (65.8)	544 (66.7)	101 (61.59)	2.0[b]
Discharge	333 (34)	270 (33.1)	63 (38.41)	
Discharge Against Medical Advice (DAMA)	2 (0.2)	2 (0.2)	0 (0.00)	

a = Pearson Chi Square test; b = Fischer exact test

Table II: Referred patients' waiting time for an ambulance at Primary Healthcare Facility (PHF)

	ALL N=980 n (%)	PRIORITY 1 N=816 n (%)	NON-PRIORITY 1 N=164 n (%)	p-value
Waiting time for ambulance at PHF (minutes)				
Mean	63	63	64	
Median	55	54	58	
Std Deviation	49	51	37	
IQR 25	37	38	37	
IQR 75	80	81	76	
Categorisation of waiting time for ambulance at PHF				
30 minutes and less	144 (14.7)	119 (14.6)	25 (15.2)	0.791[b]
More than 30 minutes to 60 minutes	397 (40.5)	335 (41.1)	62 (37.8)	
More than 60 minutes to 90 minutes	228 (23.3)	182 (22.3)	46 (28.0)	
More than 90 minutes to 120 minutes	93 (9.5)	81 (9.9)	12 (7.3)	
More than 120 minutes to 150 minutes	49 (5.0)	40 (4.9)	8.2 (3.2)	
More than 150 minutes to 180 minutes	19 (1.9)	16 (2.0)	3 (1.8)	
More than 180 minutes to 210 minutes	9 (0.9)	7 (0.9)	2 (1.2)	
More than 210 minutes to 240 minutes	6 (6.0)	5 (0.6)	1 (0.6)	
More than 240 minutes	35 (3.6)	31 (3.8)	4 (2.4)	

b = Fischer exact test

admitted to the ward (Table I). There were only two (0.2%) referred patients who requested DAMA.

Table II describes patients' waiting time for an ambulance arrival at the Primary Healthcare Facility. The mean waiting time for an ambulance is 28 minutes (SD±23), where 515 (52.6%) of them are classified as adults. An outcome of 769 (78.5%) patients received an ambulance within 90 minutes.

Table III describes basic emergency intervention received by patients in PHF prior to transfer. A total of 99% of the patients were seen in PHF with access to FBC, biochemistry and urine analysis tests. Among the patients categorised as Priority 1; 376 (46%) patients are provided with intravenous maintenance fluid, as compared to 83 (50.6%) in Non-priority 1. Ab overall of 204 (25.0%) patients triaged as Priority-1 received oxygen as compared to 26 (15.9%) in the Non-priority 1 group ($p<0.05$). There is no statistical significance between the use of intravenous fluids between the two triage groups. These interventions are started by the PHF and continued by KVAS till arrival to ED. There are 216 (26.5%) Priority 1 patients that did not receive any interventions at PHF.

Figure 1 describes the temporal distribution of patients' ambulance activation time, ED arrival time and disposition from ED time. Ambulance activation time for our patients is clustered between 11 am and 4 pm, which correlates to clinic operating hours. The median waiting time for patients in the PHF for ambulance arrival time is 54 minutes for Priority 1 and 58 minutes for Non-priority 1 triage classification. A total of 77% of patients in Priority 1 and 81% in Non-priority 1 categories have ambulance waiting time up to 60 minutes. Only 15% of patients in the Priority 1 category receive an ambulance within 30 minutes at the clinic. Patients' arrival time to the ED is clustered between 12 noon and 5 pm. Cluster

Table III: Access to investigation studies and basic emergency intervention received by patients in PHF prior to ambulance arrival.

	ALL N=980 n (%)	PRIORITY 1 N=816 n (%)	NON-PRIORITY 1 N=164 n (%)	p-value
Access blood and urine investigation at Primary Healthcare Facility (PHF)				
Full Blood Count				
Yes	975 (99.5)	812 (99.5)	163 (99.4)	1.000[b]
No	5 (0.5)	4 (0.5)	1 (0.6)	
Biochemistry test				
Yes	971 (99.1)	808 (99.0)	163 (99.4)	1.000[b]
No	9 (0.9)	8 (1.0)	1 (0.6)	
Urine analysis				
Yes	975 (99.5)	812 (99.5)	163 (99.4)	1.000[b]
No	5 (0.5)	4 (0.5)	1 (0.6)	
Basic emergency intervention received by patients at Primary Healthcare Facility (PHF)				
Oxygen therapy				
Yes	230 (23.5)	204 (25.0)	26 (15.9)	0.015[a]
No	750 (76.5)	612 (75.0)	138 (84.1)	
Intravenous fluid as bolus				
Yes	73 (7.4)	62 (7.6)	11 (6.7)	0.748[a]
No	907 (92.6)	153 (93.3)	754 (92.4)	
Intravenous fluid for maintenance				
Yes	459 (46.8)	376 (46.1)	83 (50.6)	0.304[a]
No	521 (53.2)	440 (53.9)	81 (15.5)	
No intervention received				
Yes	261 (26.6)	216 (26.5)	45 (27.4)	0.847[a]
No	719 (73.4)	600 (73.5)	119 (72.6)	

a = Pearson Chi Square; b = Fischer exact test

Table IV: Patient's length of stay in the Emergency Department (EDLOS) based on outcome, admitted or discharged

	ALL N=980 n (%)	Admitted N=645 n (%)	Discharged N=335 n (%)	p-value
Outcome of Patient in Emergency Department				
Priority 1	816 (83.3)	544 (84.3)	272 (81.2)	0.241[a]
Non-priority 1	164 (16.7)	101 (15.7)	63 (18.8)	
Total Patient's waiting time from PHF to final disposition (minutes)				
Mean	766	853	600	
Median	542	605	382	
Std Deviation	±599	±598	±565	
IQR 25	360	431	249	
IQR 75	1085	1306	746	
Patient's EDLOS (minutes)				
Mean	703	789	537	
Median	475	540	321	
Std Deviation	±600	±599	±565	
IQR 25	295	364	187	
IQR 75	1045	1240	678	
Categorisation of Patient's EDLOS				
4 hours and less	171 (17.4)	59 (9.1)	112 (33.4)	p <0.05[a]
More than 4 hours till 8 hours	320 (32.7)	212 (32.9)	108 (32.2)	
More than 8 hours till 12 hours	170 (17.3)	139 (21.6)	31 (9.3)	
More than 12 hours till 16 hours	55 (5.6)	38 (5.9)	17 (5.1)	
More than 16 hours till 20 hours	53 (5.4)	30 (4.7)	23 (6.9)	
More than 20 hours till 24 hours	74 (7.6)	51 (7.9)	23 (6.9)	
More than 24 hours	137 (14.0)	116 (18.0)	21 (6.3)	
Total patient's waiting time from PHF to final disposition in ED				
4 hours and less	112 (11.4)	38 (5.9)	74 (22.1)	p<0.05[a]
More than 4 hours till 8 hours	297 (30.3)	170 (26.4)	127 (37.9)	
More than 8 hours till 12 hours	224 (22.9)	179 (27.8)	45 (13.4)	
More than 12 hours till 16 hours	72 (7.3)	52 (8.1)	20 (6.0)	
More than 16 hours till 20 hours	51 (5.2)	31 (4.8)	20 (6.0)	
More than 20 hours till 24 hours	72 (7.3)	49 (7.6)	23 (6.9)	
More than 24 hours	152 (15.5)	126 (19.5)	26 (7.8)	

a = Pearson Chi-Square

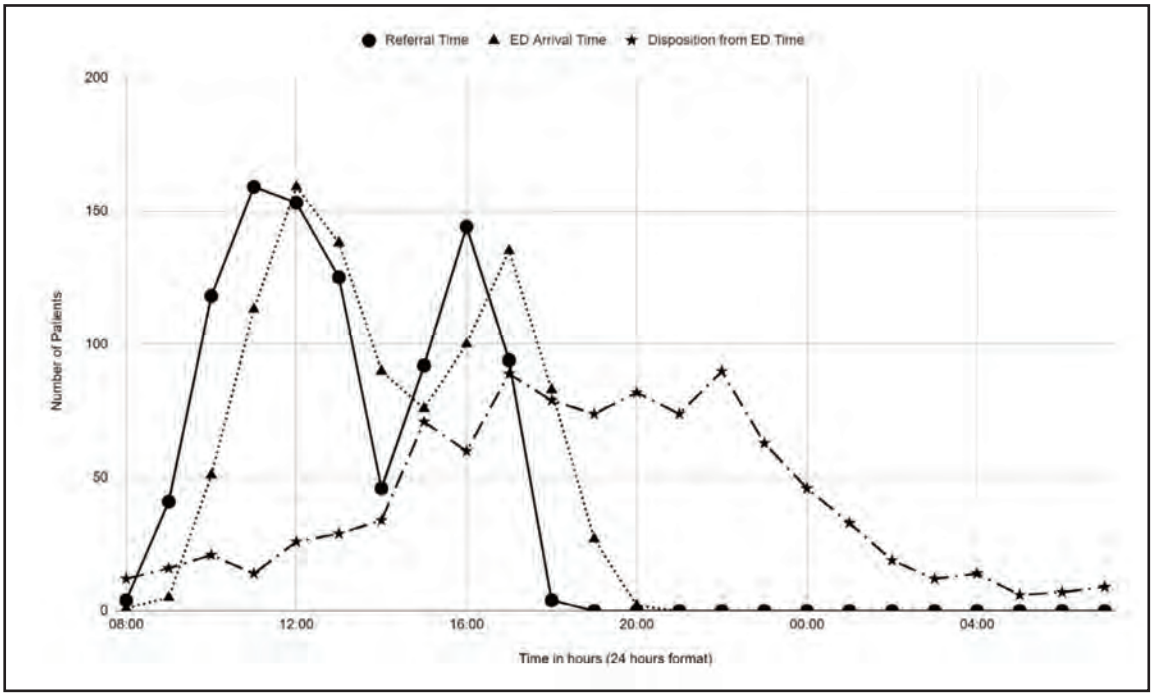

Fig. 1: Line chart showing the temporal distribution of patients' ambulance activation, arrival to the Emergency Department time and disposition from the Emergency Department time either to home or ward

of patient movement from the ED for admission in ward or discharged home occurs between 1 pm and 8 pm.

Table IV describes the EDLOS and total waiting time for patients from EMS activation till disposition from the ED. Cumulatively, 75% of patients have EDLOS up to 1085 minutes (11 hours) (mean 766 minutes, SD±599). The median EDLOS for all patients is 540 minutes (9 hours). Discharged patients have a shorter EDLOS of 321 minutes (about 5 hours). However, among discharged patients, those who request for DAMA have higher mean EDLOS of 972 minutes (16 hours). Median total patient's waiting time from PHF to final disposition is 605 minutes (10 hours) for admission compared to 382 minutes (6 hours) for patients who are discharged.

DISCUSSION

So far, there is no documented study on a patient's journey from the time an ambulance is activated in PHF till final disposition in the ED for Malaysia. This is an important marker in determining the process efficiency, case complexity and disposition outcomes among referred patients in the ED. PHF in Malaysia has two methods of ambulance activation for interfacility transfer: (a) internal activation utilising the ambulance under the command of the clinic, and (b) activating an external ambulance from either a nearby clinic or even the hospitals. We have confined our study to analysing the second method of ambulance used for the transfer under the KVAS project. In this project, affected PHF has limited or no access to their own ambulance service. Hospital Sungai Buloh receives referrals from PHF from several Public Health Districts; however, we only focus on two of KVAS operational areas, which are the Petaling Jaya area of Petaling Health District and the Sungai Buloh area of Gombak Health District. KVAS is a pilot project for the unification of ambulance service within the Ministry of Health facilities in the urban area of the central Klang Valley with the aim of better transport and logistical coordination.[11]

Priority 1 triage was assigned to 83% of patients by the PHF. Age by category and gender are not statistically significant in the determination of ambulance response triage by PHF (Table I). The aim of using a two-tier triaging system is to identify Priority-1 patients who (a) require basic emergency intervention started at PHF and subsequently continued in the ambulance and later in the ED; or (b) referrals with time-sensitive diagnosis requiring rapid transport to the hospital for timely care. Use of oxygen as an intervention was the only statistically significant difference between the triage categories. The majority of patients within the Priority-1 category received intravenous fluid, which was set as maintenance fluid. Basic emergency intervention was not required in 261 (26.6%) of patients transported by KVAS (Table II). The heavy reliance on ambulances to transfer referred patients to the hospital by PHF may be due to other non-clinical factors, such as the prevention of patients' non-compliance in going to the ED for further management and space constraints in PHF to observe patients with interventions such as intravenous fluids.

Ambulance waiting time is not statistically significant when compared with the patient's triage criteria (Table III). We found that 80% of all referrals received ambulance response time of less than 90 minutes (mean 63 minutes, median 55 minutes, SD±49). Only 14.7% of our referred patients receive an ambulance within 30 minutes. There may be several contributing factors to this: (a) the Guideline For Ambulance

Service In Primary Care by MOH Malaysia acknowledges that ambulance response in PHF is dependent to its availability on standby at the facility; (b) there is no performance measure for ambulance arrival time to PHF for Priority 1 referral patients when there is no ambulance on standby at the facility; and (c) KVAS directive sets its ambulance arrival time to PHF within 90 minutes unlike the response time set for a 999-Priority 1 case of 15 minutes.[10,11] Our team could not compare the data from PHF, which utilises its own internal ambulance team for transfers, which, to our knowledge, has never been published. MOH Malaysia needs to review its performance measurement for ambulance arrival time to PHF for referral. An example is that used by the National Health Service (NHS), United Kingdom.[12] The NHS divides ambulance response levels following assessment by Healthcare Professional (HCP) into four categories: (a) HCP Level 1 with mean response time of 7 minutes for patients in need of immediate, life-saving intervention; (b) HCP Level 2 with mean response time of 18 minute for patients requiring immediate additional clinical care in an ED or acute receiving unit; (c) HCP Level 3 with locally commissioned response for patients who need urgent assessment by specialist; and (d) HCP Level 4 with locally commissioned response who require admission but not as an emergency.[12] There are two peak times for ambulance activation by PHF, occurring at 11am and 4pm, which align with peak patient arrival times at the ED at 12 noon and 5 pm (Figure 1). This pattern corresponds with PHF's operational hours of 8 am to 5 pm. It suggests that ambulance activation timing may be influenced by operational convenience rather than by patients' clinical needs. It may also be a factor contributing to the prolonged ambulance arrival time. The distribution curve for patients' disposition time from ED has a plateau period between 5 pm and 10 pm (Figure 1). The admission rate for our study population is 65.8% (Table I), similar to that of Umgelter et al., findings of 62.6% in the metropolitan area in Germany.[13] Among the 335 (34.2%) referred patients that were discharged, we found that there is no statistical significance between the triage category of Priority 1 and non-Priority 1 by PHF. Thus far, there is no data to compare our findings of 34.2% discharge rate for PHF-referred patients. Malaysia's ED has a policy of patient boarding time of no longer than 8 hours.[4] Within the 8-hour period, 220 (65.6%) patients were able to be discharged (Table IV), and among them, 112 patients were discharged within EDLOS of 4 hours. This signifies that the majority of referred patients require further assessment and care that could not be provided at PHF. It also correlates Ang et al. (2014) and Chan et.al., an appropriate referral definition based on management capacity of the referring clinic, benefit and services received by the patient.[2,9]

We analysed patients' processing time in ED within two categories: (a) the admitted group; and (b) the discharged group, as the triaging process in ED is independent from the triage category assigned by PHF. The mean EDLOS is 537 minutes (9 hours) for the discharged group (median 321 minutes, SD±565) and 789 minutes (13 hours) for the admitted group (median 540 minutes, SD ±599 minutes) (Table IV). A total of 489 (49.9%) patients stayed in the ED for more than 8 hours before disposition occurred. A study by Ahmad Hanif et al. among walk-in patients in the ED of University Kebangsaan Malaysia Medical Centre reported a mean EDLOS of 7 hours (median 6 hours, SD 5), which is shorter than ours.[14] However, they excluded referred patients from PHF in their study population.[14] Another study by Mohammad Miqdam Abdul Aziz et al. reported a mean EDLOS of two hours (median 1 hour, SD 1) in ED Hospital Taiping among patients referred from hospitals within the Northern Perak Cluster.[15] These diverse findings of EDLOS between different cohorts of ED patients, i.e., walk-in patients, referred from PHF and referred between hospitals; suggests difference in case complexity and system processes between hospitals for admission. From the patient's perspective, total waiting time for final disposition begins from the time of ambulance activation till the time the patient physically leaves the ED. Mean total waiting time is 600 minutes (10 hours) for the discharged group (median 382 minutes, SD±565) and 853 minutes (14 hours) in the admitted group (median 605 minutes, SD±598). Hospital Sungai Buloh has a referral system that requires a Medical Officer of the referred discipline to see the patients in the ED prior to the decision for admission. Only selected disciplines, such as the critical care service for adults and neonates, have a direct admission policy. This system indirectly creates a triple layer of gatekeeping for PHF patients, beginning from FMS in PHF, to Emergency Physician in ED and finally Medical Officers of the various disciplines, again as compared to the cohort of walk-in patients of two layer of gatekeeping. It contributes to congestion in the ED, causing delay in the processing time for patient disposition, especially when the admission rate among PHF-referred patients is beyond 65%. There have been several studies looking into improving ED congestion and also the creation of a "Fast-Track Referral System" as one of the interventions.[7,16] Our findings support the implementation of a dedicated "Fast-Track Referral System" which incorporates two components: (a) an education system with a structured referral communications sheet for PHF; and (b) an enhanced multidisciplinary coordination process within the ED.[7,16] Such system will improve patient flow, improve resource utilisation and reduce unnecessary delays in ED. It will also reduce the overall referred patients' total waiting time.

Our data of ambulance transfer time in this study is reviewed only from the perspective of PHF that utilises an external source of ambulance from KVAS in its first six-months of the pilot project. Further study is needed to analyse the ambulance waiting time comparison for patient transfer between PHF that activates its own ambulance team and that of an external team. Our EDLOS data investigated the system implemented by a single tertiary centre, which may differ from other hospitals. Furthermore, we did not include details on interventions received by referred patients in the ED, their vital parameters upon arrival at the ED and the clinical syndrome which they were treated for. Incorporating these factors could enhance understanding and improve the 'model of care pathway' for referral patients. It is beyond the scope of our study and the available data analysis to provide insight into ED overcrowding factors and the cost-effectiveness of our proposed solutions.

CONCLUSION

This study describes the journey of referred patients from PHF, beginning from the point of ambulance activation till they physically leave the ED. The admission rate in the study population is 65.8%. Mean EDLOS for all patients is 12 hours, which is beyond the ED policy of 8 hours, which suggests a significant access block. The mean total time spent by patients from PHF till ED disposition of 13 hours suggests that there is a need to have a "Fast-Track Referral System". Additional gatekeeping process within the hospitals for referrals from PHF is redundant, as only 22.4% of total referred patients can be discharged from the ED within 8 hours.

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ORIGINAL ARTICLE

Survey of virtual ward acceptance among medical patients admitted to hospital

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ABSTRACT

Introduction: Virtual ward (VW) is a hospital-led alternative to inpatient care enabled by technology where patients are looked after in their usual residence. Such a service may not be familiar to many. This survey aims to explore the views and acceptability of VW among hospitalised patients.

Materials and Methods: This study was conducted among patients aged ≥18 years admitted to medical wards of a tertiary hospital in Malaysia. The survey questions were adapted from existing questionnaires and piloted before use. Participants were provided with a clinical vignette and description of a VW service before completing the questionnaire. It collated data on respondents' demographics, admission details, VW acceptability and their views on VW-related telehealth. The next of kin or main caregiver provided responses if the person was unable to participate.

Results: Responses were collected from 120 participants (95 patients, 25 caregivers), of which 108 respondents (90.0%) agreed to be managed by a VW service if such a service was available and able to meet their needs. Being at home, supported by family members, and the ability to maintain independence were the most common reasons cited for its acceptance. Among those unwilling, participants preferred to have the medical and nursing team close by. In terms of telehealth readiness, 95% of patients have internet access, and 97.5% possess the appropriate devices for video consultation. However, only 20% of patients have utilised online video consultations before to seek medical advice.

Conclusion: The majority of people surveyed were willing to accept a virtual ward service. The findings provide useful information towards the planning of virtual ward programmes in Malaysia.

KEYWORDS:
Virtual, hospital, telehealth, telemedicine

INTRODUCTION

A virtual ward (VW) is a hospital-led alternative to inpatient care that is enabled by technology.[1] Through the use of remote monitoring and telecommunication, VWs facilitate the delivery of comprehensive hospital-level care, encompassing physician consultations, medication administration, nursing and therapy services, clinical diagnostics, and investigations, among other essential healthcare provisions. Hospital teams rely on carers and family members to support elements of care in the home, with clinical oversight provided remotely. The technology used in VW can also complement the delivery of hospital-at-home services that provide face-to-face care at the person's home through multidisciplinary teams as a substitute for inpatient care. As a result, hospital admissions may be avoided altogether or inpatient stays shortened through earlier discharge.

The COVID-19 pandemic served as a catalyst for the development, adoption, and expansion of VWs. Patients could be effectively and safely managed at home remotely.1 VW initiatives have been established in countries, such as Australia, the United States, Canada, the United Kingdom, and Spain.[2] For many, VWs were implemented as part of a broader hospital-at-home service. Research findings indicate that the adoption of such services lead to potentially better clinical outcomes, such as shorter hospital stays and decreased rates of readmission.[3] The mortality rates observed were comparable to those of patients admitted to conventional hospital wards.[4] VWs could alleviate mental stress and mitigate adverse hospital events, including functional decline, incontinence, and delirium, among older individuals undergoing acute hospital admissions.[5-7] Hence, many have considered VWs as a safe and effective alternative to address the overwhelming burden placed on acute hospitals.

The growing acceptance of telehealth, tele-consultations and digital monitoring of health conditions among healthcare professionals suggests that the healthcare landscape may be ready to adopt VWs. This is also supported by wider internet coverage, smart device penetration, and devices with better phone and video capability. However, whether VWs is an acceptable model of care for the wider public is uncertain. Using technology to support acute care being delivered outside hospitals remains unfamiliar to many. Therefore, this survey aims to explore the perception and acceptability of VWs among hospitalised adult patients in a tertiary hospital.

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Table I: Demographic and characteristics of respondents (n=95)

Demographic and clinical variables	
Age, mean (SD), years	44.0 (16.6)
Age ≥65 years, n (%)	12 (12.6)
Men, n (%)	49 (51.6)
Ethnicity, n (%)	
Malay	57 (60.0)
Chinese	21 (22.1)
Indian	17 (17.9)
Employment status, n (%)	
Employed full time	43 (45.3)
Employed part time	2 (2.1)
Self employed	14 (14.7)
Unemployed	8 (8.4)
Retired	28 (29.5)
Housing type, n (%)	
Multi-storey house	31 (32.6)
Single-storey house	22 (23.2)
Flat/apartment/condominium with lift	28 (29.5)
Flat/ apartment/ condominium without lift	12 (12.6)
Others	2 (2.1)
Education level, n (%)	
Primary	5 (5.3)
Secondary	31 (32.6)
Pre-university	10 (10.5)
Diploma	18 (18.9)
Degree	30 (31.6)
No formal education	1 (1.0)
Living with, n (%)	
Spouse	31 (32.6)
Spouse and children	20 (21.0)
Parents	24 (25.2)
Children	4 (4.2)
Friends	5 (5.3)
Live alone	3 (3.2)
Paid caregivers	1 (1.1)
Others	7 (7.4)
Mobility before admission, n (%)	
Walks without aid	83 (87.4)
Walks with aid	10 (10.5)
Using wheelchair to get around	2 (2.1)
Daily Activities, n (%)	
Can do both basic and complex daily activities alone	86 (90.5)
Needs some help with basic daily activities	7 (7.4)
Can do basic daily activities alone only independently	2 (2.1)
Diagnosis category*, n (%)	
General medical diseases	37 (39.0)
Gastrointestinal diseases	14 (14.7)
Neurological diseases	13 (13.7)
Respiratory diseases	11 (11.6)
Endocrine/metabolic diseases	8 (8.4)
Infectious disease	6 (6.3)
Others	6 (6.3)

*Based on which ward or specialty disposition

MATERIALS AND METHODS

This survey was conducted among patients aged ≥18 years admitted to the medical wards of a university hospital in Malaysia between 1 July 2024 and 16 August 2024. Patients who were unable to provide informed consent independently had their next of kin or caregivers invited to participate on their behalf. The caregiver was defined as the main or nominated spokesperson for the family. The survey excluded those who were critically unwell, terminally ill, or have isolation precautions (e.g., respiratory precautions).

The study questionnaire was adapted from two previously used questionnaires. The previously used questionnaires assessed acceptance of hospital-at-home services (in a Singapore setting), which share many similarities with VWs, and virtual consultations (conducted within the same institution as this study).[8,9] Minor contextual modifications were made by the research team to align itself with the proposed hospital's VW services. The adapted questionnaire domains included: (a) demographic information, (b) acceptability, (c) views on telehealth, (d) perceptions of healthcare delivered at home, (e) views on payment for VW,

Table II: Characteristics of the caregivers (n=25)

Caregivers, n (%)	
Age, mean (SD), years	54.2 (12.8)
Employment status	
Employed full time	7 (28.0%)
Employed part time	2 (8.0%)
Self employed	1 (4.0%)
Unemployed	8 (32.0%)
Retired	7 (28.0%)
Educational level	
Secondary education	8 (32.0%)
Pre-university	1 (4.0%)
Diploma	4 (16.0%)
Degree and above	8 (32.0%)
No formal education	1 (4.0%)
Declined to answer	3 (12.0%)
Work From home option	
Yes	3 (12.0%)
No	6 (24.0%)
Not applicable	16 (64.0%)
Caregiver relationship with patient	
Child	10 (40.0%)
Spouse	7 (28.0%)
Parent	4 (16.0%)
Paid caregiver	1 (4.0%)
Grandchild	1 (4.0%)
Other	2 (8.0%)

and (f) admission details. For participants who were unable to answer the survey but fulfilled the eligibility criteria, the survey form was adapted to gather the caregiver's views. To assess acceptability and gather respondents' views on a VW service, a brief description of the service was explained to the participants prior to the start of the survey.

The sample size for this survey was determined by the primary outcome of the proportion of patients that would accept a VW care if offered based on a previously conducted survey.[8] To provide a 95% confidence level of and a margin of error of 10%, assuming that there would be an unequal proportion of patients who would accept or reject the service, this would result in a minimum sample size of 97. Taking into account potential challenges with completing the survey, the study planned to recruit 120 participants. Participants were conveniently sampled for this survey.

Patient demographics and characteristics were analysed using appropriate descriptive statistics, including frequency tabulations for categorical variables and summary parameters such as means and standard deviations for continuous variables. Acceptability was graded based on a Likert scale (Definitely no, No, Unsure, Yes, Definitely yes). The data was analysed using SPSS Version 27. Ethical approval was provided by the institution's medical research ethics committee (MREC 202431-13498).

RESULTS

A total of 155 participants were screened. Among this, 95 (79.2%) participants responded to the survey, while 25 (20.8%) caregivers responded on behalf of patients, yielding an overall response rate of 77.4%. The demographic and clinical characteristics of respondents (n=95) are detailed in Table I.

A total of 25 caregivers responded on behalf of the patients (Table II). The patients that the caregivers looked after had a mean age of 65.6 (20.7) years. The proportion ≥65 years was 17/25 (68.0%). They were mostly women (13, 52%) and married (14, 56%). Among these patients, 20 (80%) lived with a family member, either children, spouse or grandchildren. Fourteen (56%) employed a domestic helper in the home, and four (16%) participants had a paid caregiver to support their personal care needs. In terms of mobility prior to admission, eight (32%) were independent with their mobility and did not require any aids, nine (36%) required walking aids with the remainder either bed or wheelchair bound. In terms of daily activity performance, nine patients (36%) were independent in both basic and complex activities, while seven (28%) required assistance with basic daily tasks, and another seven (28%) needed complete assistance. Only two (8%) were able to only perform basic daily activities independently.

Among the 120 respondents (participants who were patients and able to respond to the questions, and the caregivers of patients who were unable to participate), the majority would consider the VW as an alternative to inpatient care. 51 (42.5%) would definitely accept the service, 57 (47.5%) accept, six participants were unsure, 4 (3.3%) would not, and 2 (1.7%) definitely would not. When separated, 85/95 (89.5%) self-reporting participants, and 23/25 (92.0%) caregivers would accept such a service. The reasons for accepting or declining the VW service are summarised in Figure 1.

Regarding perceptions of telehealth use, 114 (95%) of participants had internet access and 117 (97.5%) possessed appropriate devices for video consultation. However, only 24 (20%) participants have had experience receiving medical assessment over online video consultations. 38 (31.7%) participants have utilised some form of wearable technology

to monitor health. In terms of caregivers, only nine (36%) have used online video consultation to obtain medical advice. In terms of participants' confidence in using technology to access healthcare, participants reported higher confidence in using technology to access healthcare, with 76 (63.3%) rating their confidence as "adequate" or "a lot", compared to 13 (52.0%) of caregivers.

DISCUSSION

This study demonstrated a high acceptability rate of 90% among surveyed participants to consider being managed under a VW service. Many participants displayed sufficient telehealth knowledge and had access to the necessary digital infrastructure, suggesting that VWs have the potential to support ongoing patient care. This potentially reduces the demand for hospital inpatient care. Several factors likely contributed to this high acceptance rate. Participants expressed a strong preference to remain at home when clinically appropriate, with their care and recovery supported by family members. They reported that this would better facilitate their recovery and preserve their independence.

Several factors from this survey may explain the high acceptance rates. Many respondents were relatively younger, and possibly more technology literate to be receptive to digital health solutions.[8,10] Participants also reported high rates of internet access and device ownership which could influence the acceptance of VW services. Additionally, most participants already have support at home to enable care. The high acceptance was also reported by caregivers. Although this study was not designed to explore the reason behind this, it is plausible that the high acceptance can be contextualised by strong sociocultural norms around family involvement in care, including multigenerational cohabitation and expectations of filial caregiving.[11] These family-centred structures may enhance acceptability of home-based care which fits with the preference to avoid or minimise hospitalisation.

Being at home may also facilitate recovery, as evidenced in existing literature. Levine et al., demonstrated in a randomised controlled trial that patients managed at home had significantly lower 30-day readmission rate compared to their controls (7% vs. 23%).[3] Similarly, studies conducted during the COVID-19 pandemic by Ward et al. and Grutters et al., highlighted the safety and efficacy of VW.[12,13] These investigations on home telemonitoring for COVID-19 patients reported low readmission rates of 3% and 9%, respectively, with Ward et al., noting a 1% mortality.[12] Collectively, these findings support the potential of VW to ensure patient recovery in managing acute illness outside traditional hospital environments. VW provides the opportunity to maintain a level of independence while still receiving necessary medical oversight. Hospitalised patients often experience prolonged sedentary periods, with studies showing that 90% of their hospital stays are spent in low-activity states, which can lead to decreased mobility and greater dependency post-discharge.[14,15] Familiar home environments have a profound impact on sleep and appetite, which are both vital to ensure recovery.[16] This context highlighted the psychological and physical benefits of VWs.

VWs offer the opportunity to extend hospital-level care into patient's homes, while reducing the likelihood of hospital-acquired infections, falls and fostering more personalised patient-centred care. Findings from this survey provide an important baseline for future targeted studies aimed at better understanding specific factors which may influence VW acceptance among patients and caregivers in similar healthcare systems and region. Studies across various countries, including the United Kingdom, United States, Australia, Canada, and Singapore have similarly demonstrated the possible reasons of acceptance of virtual is due to their immense benefits such as increased convenience, reduced travel time, cost, and earlier discharge time, indicating the potential of VWs to improve healthcare delivery in diverse healthcare system.[8,17-20] Studies by both Heller et al. and Coloma et al. supports this potential, showed that shifting dependency on hospital-centric care models can rapidly expand bed capacity and reduce nosocomial infection risks.[21,22] Key reasons for acceptance were reported in a study by Lai et al. in Singapore which surveyed hospitalised patients (mean age 53.5, SD 15.3) showed a 72.5% acceptance rate for such a service.[8] The primary reasons for acceptance included comfort at home, the presence of family members, and confidence in remote monitoring systems. Another pilot study during the COVID-19 pandemic demonstrated high acceptance of virtual consultations adult caregivers, though it focused on older outpatients, which limits direct comparison to our inpatient sample.[9] Acceptance was particularly high among those with electronic devices, living companions, or familiarity with virtual platforms which mirrors findings from this survey.

Despite the high overall acceptance of VWs identified in this study, only one-in-five of participants have experience with online video consultations for healthcare purposes, and just under one-third have used wearable health-monitoring devices. Over one-third of caregivers had accessed medical advice via video consultation. This low baseline digital health engagement may represent an important barrier to VW implementation and scalability, underscoring the need for targeted digital literacy support, caregiver training, and system-level facilitation to support future implementation.

This study has several limitations. It consisted of relatively young respondents, which may not accurately reflect the broader age distribution of hospitalised patients. Older adults may face challenges completing this survey independently, and not all have a caregiver available to respond on their behalf. Many VW or hospital-at-home services in published literature have been designed to meet the needs of older adults.[2] However, this should not exclude the views of younger individuals. While they may not represent those with the highest healthcare needs, their perspectives remain relevant, as they are also likely to benefit from VW services. This use of convenience sampling introduces potential sampling and reporting biases. Nearly 30% of approached patients declined participation, which may have skewed results if these individuals were less inclined to accept VW services. Besides that, this hospital served an urban catchment area which limits how a VW service would be accepted in other areas. This study was unable to identify any demographic or socioeconomic factors that might influence

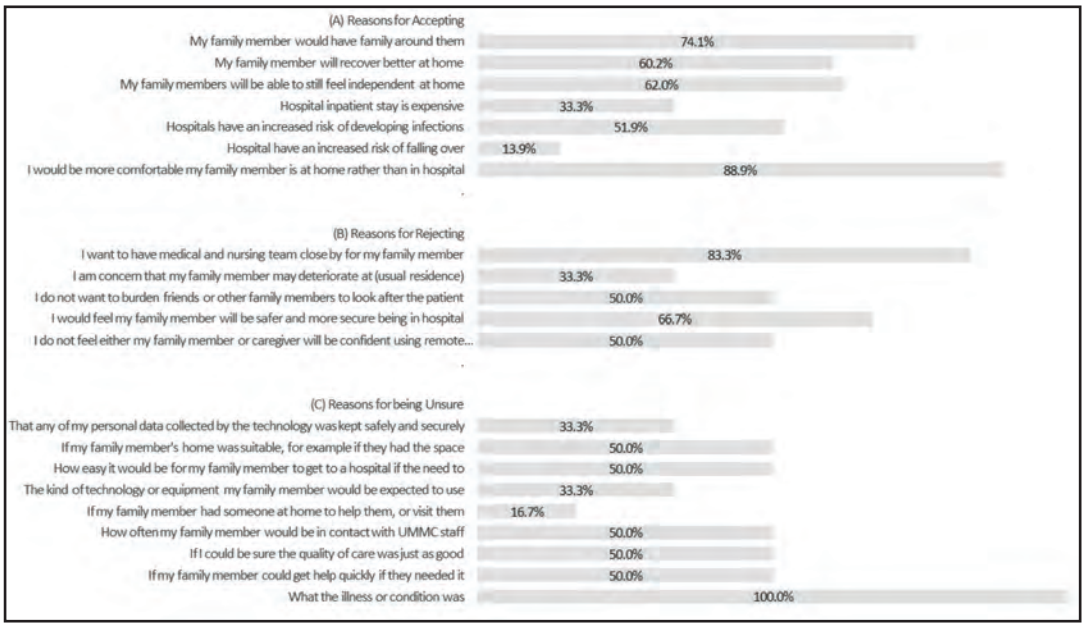
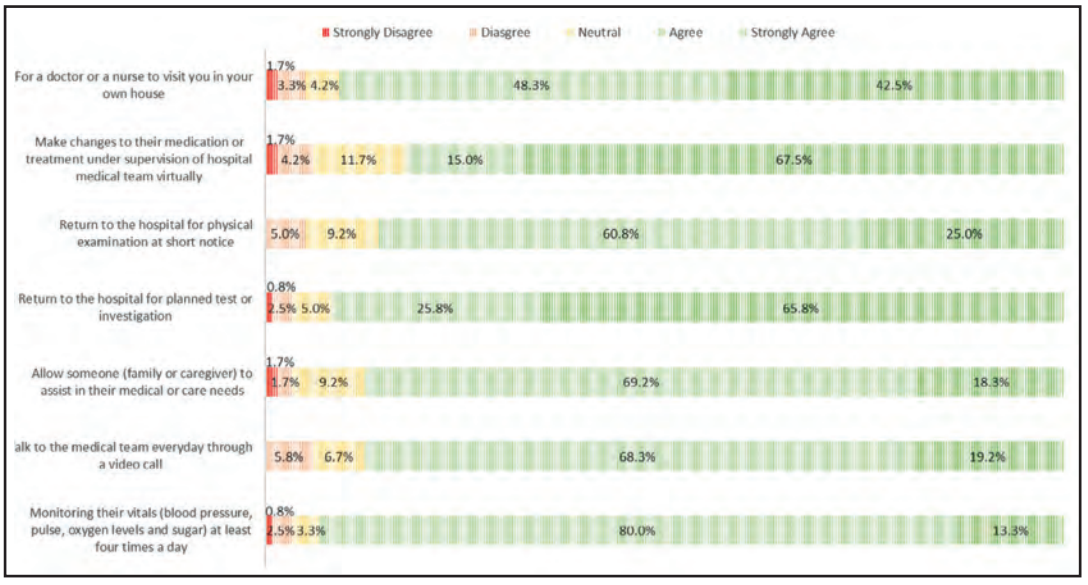


Fig. 1: Reasons for (A) Accepting, (B) Rejecting, and (C) Unsure of the virtual ward service



Participants expressed their willingness to accept individual components offered by a VW service (Figure 2).

Fig. 2: Acceptance of individual components within a virtual ward service

VW acceptance. The quantitative nature of the survey with its limited range of answer choices was unable to fully explore patients' reasons for accepting or declining VWs. Therefore, these limitations do affect the results and ultimate generalisability of this study's findings. The study sample would have systemic differences with the general population that VW services would target. Despite these limitations, the findings from this study provided valuable insight into the community's acceptance of VW services in Malaysia.

Several recommendations for future studies on VW acceptance. A broader age demographic and clinical needs will provide a more representative understanding of acceptance across age groups particularly among those with the highest healthcare needs. To reduce sampling and reporting biases, future studies could adopt stratified sampling methods across different settings to increase representativeness and reduce biases. Future surveys could include more comprehensive and detailed questions to explore motivations and barriers, with open-ended questions allowing for better insights. Long term studies might be helpful to understand how acceptance and usage of VWs evolve over time, especially in relation to patient satisfaction, health outcomes and cost effectiveness.

CONCLUSION

This study is the first to assess patient and caregiver acceptance of VW services in Malaysia, demonstrating a high acceptability rate. This readiness stems from a relatively younger, digitally enabled demographic and a cultural preference for family-supported home care. Despite its limitations, the study underscores the promise of VWs as a mainstream healthcare model. Moving forward, sustainable funding and targeted outreach are crucial to broaden access, while future research should explore acceptance across diverse demographics to support the scalability of VWs in Malaysia. Adopting this model could play a vital role in the evolution of accessible, efficient healthcare.

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ORIGINAL ARTICLE

Genomic profiling of early-stage resectable non-small-cell lung cancer in a Malaysian private healthcare setting: Real-world clinical implications

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ABSTRACT

Introduction: The prevalence of oncogenic driver mutations in early-stage resectable non-small-cell lung cancer (rNSCLC) in Malaysia remains unknown. This information may guide treatment decisions, especially tyrosine kinase inhibitor (TKI) use. We characterised the genomic landscape of early-stage NSCLC in a surgical cohort and explored its impact on TKI administration, particularly osimertinib.

Materials and Methods: 146 patients who underwent curative resection for early-stage rNSCLC were included in this study. Real-time polymerase chain reaction (PCR) and next-generation sequencing (NGS) were used to identify genetic alterations in tumour samples. Associations between EGFR status and clinico-pathological characteristics were analysed using uni- and multivariate logistic regression.

Results: A majority of patients were female non-smokers of Chinese ethnicity with an incidental adenocarcinoma. EGFR mutations were detected in 62.3% (n=91) of patients, with 93.4% harbouring single-locus mutations, primarily in exons 19 and 21. Co-mutations occurred in 11% (n=10) of EGFR-mutant cases, most frequently involving TP53, and less commonly CTNNB1, HER2/ErbB2, and PTEN. Six (6.6%) patients had multi-loci EGFR mutations. Female sex and higher tumour histological grade were independent predictors for EGFR mutations, while former/never smokers showed higher odds on univariate analysis. Among patients tested for PD-L1 (78.8%), 46.6% had negative expression (tumour proportion score <1%), with no correlation to EGFR status.

Conclusion: This is the first genomic molecular profiling study to report exclusively on early-stage NSCLC in Malaysia. The high prevalence of EGFR mutations observed, predominantly involved sensitizing mutations at exons 19 and 21, and was associated with the female sex, a non-smoking status, higher tumour grade, but not PD-L1 expression. Early reflex genomic testing is vital to guide biomarker-driven peri-operative treatment strategies for rNSCLC.

KEYWORDS:
Early-Stage resectable NSCLC, Genomic Landscape, EGFR

INTRODUCTION

The treatment paradigm for early-stage resectable non-small-cell lung cancer (rNSCLC) has evolved considerably in recent years, particularly with the adoption of peri-operative systemic therapies and the integration of genomic insights into treatment planning. The incorporation of immune checkpoint inhibitors (ICIs) peri-operatively has improved patient outcomes with significant improvements in pathological complete response (pCR) rates that correlate with enhanced event-free survival (EFS), overall survival (OS) and reduced risk of recurrence for patients without driver mutations. Adjuvant administration of tyrosine kinase inhibitors (TKIs) has resulted in superior disease-free survival (DFS) and OS for patients with tumours harbouring actionable driver mutations.[1] Understanding tumour biology is now pivotal in selecting optimal bespoke treatment modalities, however, there remains a notable paucity of comprehensive genomic data for early-stage rNSCLC, in specific populations. This gap hampers the development of tailored treatment strategies and underscores the need for further research. Ongoing efforts to map the genomic landscape will help refine and personalise treatments, ultimately enhancing patient outcomes.

MATERIALS AND METHODS

Patients and data collection

This observational study utilized a universal sampling

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approach to retrospectively analyse 146 primary NSCLC patients who underwent curative resection from January 2021 to June 2025, at two private hospitals in Greater Kuala Lumpur, Malaysia. All patients were clinically staged pre-operatively with a PET-CT scan, and if indicated, a contrasted MRI brain scan. Demographic and clinico-pathologic data were collected from both physical and electronic medical records.

Surgical procedure
The standard operation in all patients was a curative-intent anatomical resection (lobectomy or segmentectomy) with concurrent systematic mediastinal lymph node dissection, performed with a minimally invasive uniportal approach under single lung ventilation general anaesthesia.

Tissue sampling and processing
Tissue samples were obtained by computed tomography (CT)-guided transthoracic needle biopsy or from the resected surgical specimen, then processed and preserved in formalin-fixed, paraffin-embedded (FFPE) tissue blocks.

Molecular testing and analysis
Next-generation sequencing (NGS) was used to identify genetic mutations and alterations. Programmed death-ligand 1 (PD-L1) expression was tested using the Dako 22C3 antibody on the Autostainer Link 48. The tumour proportion score (TPS) was used for reporting, indicating the percentage of tumour cells with membranous staining. Tests were performed in an ISO and CAP-certified laboratory.

Statistical analysis
Statistical analyses were performed using GraphPad Prism 10.0 and Jamovi (version 2.6.4). Descriptive statistics were used to analyse the demographic data. Continuous variables were presented as means, while categorical data were presented as frequencies or percentages. Logistic regression analysis was performed to identify predictors for an EGFR mutation. A p-value <0.05 was considered statistically significant.

RESULTS

Patient demographics and tumour characteristics
All patients but one had curative R0 resections with clear microscopic margins. There was no operative, in-hospital or 90-day mortality. Of the 146 patients evaluated, the mean patient age was 60.9 years, with a majority being females (n=81, 55.5%), of Chinese ethnicity (n=113, 77.4%) and never-smokers (n=102, 69.9%) (Table I). Ninety-five (65.1%) patients were asymptomatic with an incidental or screening-detected NSCLC. Patients who were symptomatic presented with cough, haemoptysis, weight loss, shortness of breath or chest pain. The predominant histology was adenocarcinoma in 141 (96.6%) patients (Table II). Of the 146 patients, 51 (34.9%) were diagnosed at stage IA, followed by stage IB (18.4%), stage IIA (14.4%), stage IIB (15.8%), stage IIIA (13.7%), and stage IIIB (2.8%). More than half of the patients (53.4%) had moderately differentiated (Grade II) tumours, followed by Grade I (34.9%) and Grade III (11.7%). In terms of tumour invasiveness, 37 (25.3%) patients had microscopic lymphovascular invasion (LVI), while visceral pleural invasion (VPI) (19.2%) and tumour spread through air space (STAS) (15.8%) were also reported, albeit at a lower rate. There were no microscopic features of tumour invasiveness in the remaining patients.

Overall mutational landscape, single gene mutation, and co-mutation profiles
The most common mutation detected in this study involved the EGFR gene, which was observed in 91 of 146 patients with a frequency of 62.3%. The next most frequent mutations were: TP53 (16.4%), HER2/ErbB2 (6.1%), ROS1 (5.5%), and ALK and RAS (4.8% each) (Figure 1(a)). The majority of the patients harboured a single gene mutation; EGFR mutations were the most frequent, identified in 71 patients (68.3%), followed by ROS1 (7.7%), ALK (6.7%), KRAS (5.7%), TP53 (5.7%), and other less commonly mutated genes (Figure 1(b)).

Co-mutations involving more than one gene were present in 26 of the 146 study patients (17.81%). The genes which co-mutated with EGFR include TP53 (10), CTNNB1 (3), HER2/ErbB2 (2), KEAP1 (1), PTEN (1) and NRAS (1) (Figure 2(a)). Another notable co-mutation pair was HER2/ErbB2 and TP53, present in 5 out of 7 patients who tested positive for HER2/ErbB2 mutations. Notably, 2 patients harboured two or more co-mutations, namely EGFR-TP53-FGFR2 and EGFR-TP53-PTEN-CDK4.

EGFR gene mutation subtypes
Exon 19 deletion and exon 21 L858R missense mutation were the most common, making up 84.6% of all the EGFR mutations detected in this study (Figure 2(b)). Other subtypes detected were exon 18 missense (5.2%), exon 20 insertion (4.1%) and exon 20 missense (T790M) (3.1%). The prevalence of rarer mutation subtypes such as exon 21 missense (L861Q), exon 19 insertion and exon 19 missense (I744M) was 1% each.

Univariate and multivariate logistic regression analysis for predictors of EGFR mutation
All 91 of our EGFR-mutated patients in this study had adenocarcinoma histology. The clinico-pathological characteristics of EGFR-mutated and EGFR-wild type patients are summarised in Table II. At univariate analysis, female gender, a former/never smoker status and tumour histological grade (grade III) were associated with a higher odds for harbouring an EGFR mutation (Table III). However, on multivariate analysis, only being female and a higher tumour grade were predictive (Table III). Although having a grade III tumour was significantly associated with EGFR mutation in both the univariate and multivariate models, the wide confidence interval (Table III) and the small number of cases (n=4) warrant cautious interpretation. (Tables II and III).

PD-L1 expression
PD-L1 testing was done in 115/146 (78.8%) of patients, either pre-operatively on the CT-guided diagnostic biopsy sample or on the resected surgical specimen. In patients who underwent PD-L1 testing, 68 (46.6%) had a negative score (TPS < 1%), 38 (26%) had a low score (TPS 1-49%), and 9 (6.2%) patients had a high expression (TPS > 50%) (Table II).

Table I: Demographics, smoking status, personal and family cancer history according to EGFR status

Baseline Characteristics	All patients n = 146	EGFRm n = 91	EGFRwt n = 55
Age in years (mean ± S.D.)	60.9 ± 10.0	60.5 ± 9.2	61.6 ± 11.1
Age category (number (n), percentage (%))			
< 60	61 (41.8)	44 (48.3)	17 (30.9)
60-79	83 (56.9)	47 (51.7)	36 (65.5)
≥ 80	2 (1.3)	0 (0)	2 (3.6)
Gender (n, %)			
Male	65 (44.5)	30 (33.0)	35 (63.6)
Female	81 (55.5)	61 (67.0)	20 (36.4)
Race/ ethnicity (n, %)			
Malay	9 (6.2)	6 (6.6)	3 (5.5)
Chinese	113 (77.4)	69 (75.8)	44 (80.0)
Indian	10 (6.9)	5 (5.5)	5 (9.0)
Others	14 (9.5)	11 (12.1)	3 (5.5)
Smoking status (n, %)			
Current	16 (11.0)	4 (4.4)	12 (21.8)
Former	28 (19.1)	17 (18.7)	11 (20.0)
Never	102 (69.9)	70 (76.9)	32 (58.2)
Presenting symptoms (n, %)			
Asymptomatic	95 (65.1)	62 (68.1)	33 (60.0)
Cough	33 (22.6)	19 (20.9)	14 (25.5)
Hemoptysis	13 (8.9)	7 (7.7)	6 (10.9)
Weight loss	6 (4.1)	4 (4.4)	2 (3.6)
Shortness of breath	5 (3.4)	4 (4.4)	1 (1.8)
Chest pain and discomfort	5 (3.4)	3 (3.3)	2 (3.6)
Back pain and body ache	2 (1.4)	2 (2.2)	0 (0)
Dizziness	1 (0.7)	1 (1.1)	0 (0)
Palpitations	1 (0.7)	0 (0)	1 (1.8)
Personal cancer history (n, %)			
Yes	19 (13.0)	11 (12.1)	8 (14.6)
No	110 (75.3)	69 (75.8)	41 (74.5)
N/A	17 (11.7)	11 (12.1)	6 (10.9)
Family cancer history (n, %)			
Yes	49 (33.6)	34 (37.4)	15 (27.3)
No	80 (54.8)	44 (48.4)	36 (65.4)
N/A	17 (11.6)	13 (14.2)	4 (7.3)

EGFRm= EGFR mutation detected; EGFRwt= EGFR wild type; S.D.= Standard Deviation, N/A= not available

DISCUSSION

EGFR prevalence and reflex testing

NSCLC remains a major cause of cancer-related mortality globally. Sixty per cent of both new cases and mortalities occur in Asia, whilst in Malaysia, it is the second and third most prevalent male and female cancer respectively.[2] It is the most common cause of cancer-related mortality in Malaysian men, and in women, only breast cancer has a more fatal outcome. Approximately 30% of all NSCLC cases are amenable to surgery, offering the best long-term prognosis in terms of EFS, DFS and OS when combined with multimodal therapy. However, in Malaysia, lung cancer outcomes are particularly poor, with 95% of cases presenting at advanced stages. A considerable number of surgical patients will experience stage-dependent local or distant relapse due to micro-metastases. Despite surgery and adjuvant platinum-based chemotherapy (PBC), the five-year OS benefit over surgery alone remains modest at approximately 5%.[3,4]

EGFR mutation prevalence in Malaysia

Local genomic data in early-stage NSCLC is limited. Prior studies in Malaysian patients involved mostly stage III-IV adenocarcinoma, with reported EGFR mutation frequencies ranging from 39.5% to 46.5% with higher prevalence in females, never-smokers, and ethnic Chinese.[5,6] Our study observed an EGFR prevalence of 62.3%, exceeding previous local and regional reports, likely reflecting our patient composition of predominantly female, ethnic Chinese, non-smoking patients with earlier-stage adenocarcinoma. Globally, the prevalence of EGFR mutations varies widely, from 14.1% in Europe to 49.1% in Asia.[7-11] The EARLY-EGFR study demonstrated regional differences, with Singapore and Thailand reporting rates above 60%.[11] In our cohort, the majority of EGFR mutations were actionable: exon 19 deletions or exon 21 L858R missense mutations, consistent with patterns reported elsewhere.[11,12] In one study, the TP53 gene was the most common co-mutation identified, similar to our findings.[6]

The high proportion of druggable EGFR mutations (84.7%) underscores the need for reflex genomic testing at the start of the patient journey, upon initial histological diagnosis. Reflex testing expedites treatment planning, shortens turnaround times, and ensures patients receive timely,

Table II. Tumour characteristics according to EGFR status

Tumour characteristics	All patients n = 146	EGFRm n = 91	EGFRwt n = 55
Type of tumour (n, %)			
Squamous Cell Carcinoma	4 (2.7)	0 (0)	4 (7.3)
Adenosquamous Carcinoma	1 (0.7)	0 (0)	1 (1.8)
Adenocarcinoma	141 (96.6)	91 (100.0)	50 (90.9)
Pathologic stage (n, %)			
IA	51 (34.9)	36 (39.5)	15 (27.3)
IB	27 (18.4)	17 (18.7)	10 (18.2)
IIA	21 (14.4)	13 (14.3)	8 (14.5)
IIB	23 (15.8)	12 (13.2)	11 (20.0)
IIIA	20 (13.7)	12 (13.2)	8 (14.6)
IIIB	4 (2.8)	1 (1.1)	3 (5.5)
Tumour grade			
Well differentiated (I)	51 (34.9)	38 (41.8)	13 (23.6)
Moderately differentiated (II)	78 (53.4)	49 (53.8)	29 (52.7)
Poorly differentiated (III)	17 (11.7)	4 (4.4)	13 (23.7)
Tumour invasiveness			
Lymphovascular invasion	37 (25.3)	22 (24.2)	15 (27.3)
Spread through air space	23 (15.8)	13 (14.3)	10 (18.2)
Visceral pleural invasion	28 (19.2)	18 (19.8)	10 (18.2)
PD-L1			
Negative (TPS < 1%)	68 (46.6)	46 (50.5)	23 (41.8)
Low (TPS 1-49%)	38 (26.0)	22 (24.2)	15 (27.3)
High (TPS > 50%)	9 (6.2)	5 (5.5)	3 (5.5)
Not tested	31 (21.2)	18 (19.8)	14 (25.4)

PD-L1= Programmed Death-Ligand 1, TPS= Tumour Proportion Score

Table III: Univariate and Multivariate Logistic Regression Analysis of Predictors for EGFR Mutation in NSCLC Patients
Univariate Logistic Regression Analysis

Characteristic/ Variable	Odds Ratio (OR)	95% CI for OR		p-value
		Lower	Upper	
Age in years (mean, S.D.)				0.7224
Sex				
Female (vs male)	3.56	1.803	6.956	0.0005*
Race/ethnicity				
Malay	N.E.	-	-	-
Chinese	1.275	0.3401	4.836	> 0.999
Indian	2.000	0.3611	10.31	0.6499
Others	0.546	0.1037	3.001	0.6430
Smoking status				
Current	N.E.	-	-	-
Former	0.2157	0.066	0.7812	0.031*
Never	0.1524	0.052	0.4736	0.0015*
Cancer history				
No personal cancer history (vs personal cancer history)	0.8170	0.2955	2.227	0.7990
No family cancer history (vs family cancer history)	1.855	0.8582	3.819	0.1378
Pathologic stage				
IB (vs IA)	1.412	0.5586	3.863	0.6111
IIA (vs IA)	1.477	0.4698	4.079	0.5799
IIB (vs IA)	2.200	0.8391	5.724	0.1878
IIIA (vs IA)	1.600	0.5351	4.555	0.4109
IIIB (vs IA)	7.200	0.9670	95.52	0.0975
Tumour grade				
Well differentiated (I)	N.E.	-	-	-
Moderately differentiated (II)	1.730	0.8165	3.763	0.1836
Poorly differentiated (III)	9.500	2.620	29.27	0.0003*
Tumour invasiveness				
Lymphovascular invasion	N.E.	-	-	-
Spread through air space	1.128	0.3968	3.100	>0.999
Visceral pleural invasion	0.8148	0.3057	2.343	0.7988
PD-L1				
High	N.E.	-	-	-
Low	1.136	0.2315	4.790	> 0.999
Negative	0.8333	0.1912	3.373	> 0.999

S.D.= Standard Deviation, N.E.= Not evaluable
* Statistically significant (p < 0.05)

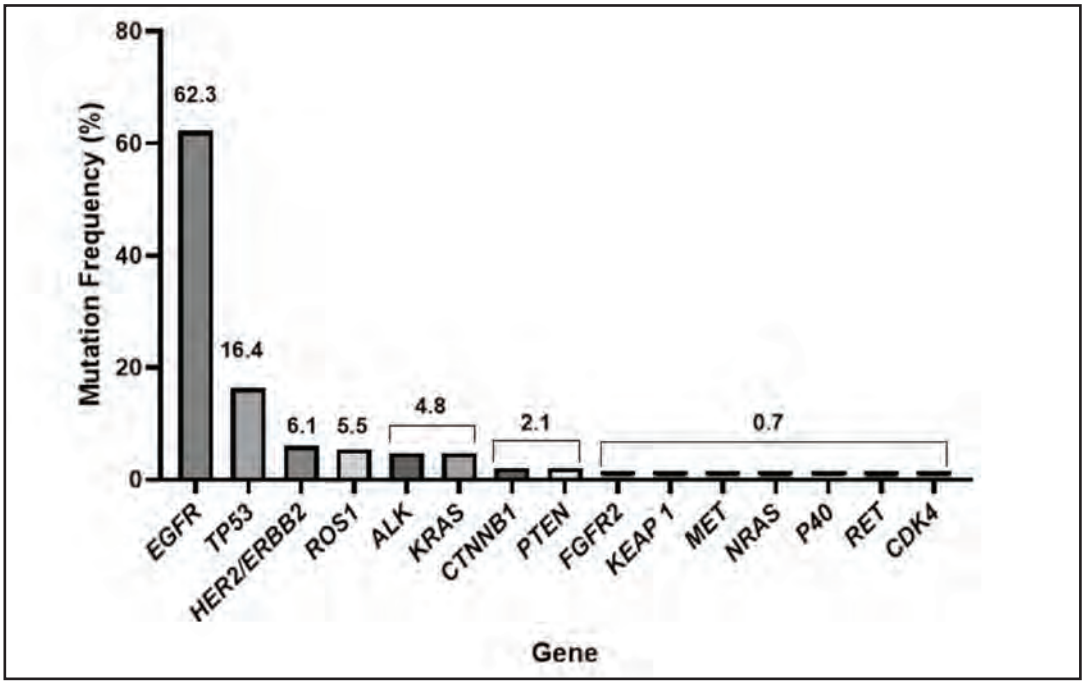

Fig. 1: A) Percentage frequency of gene mutations detected in early-stage, resectable NSCLC patients. Each bar represents the proportion of patients carrying mutations (mutant) for the respective genes.

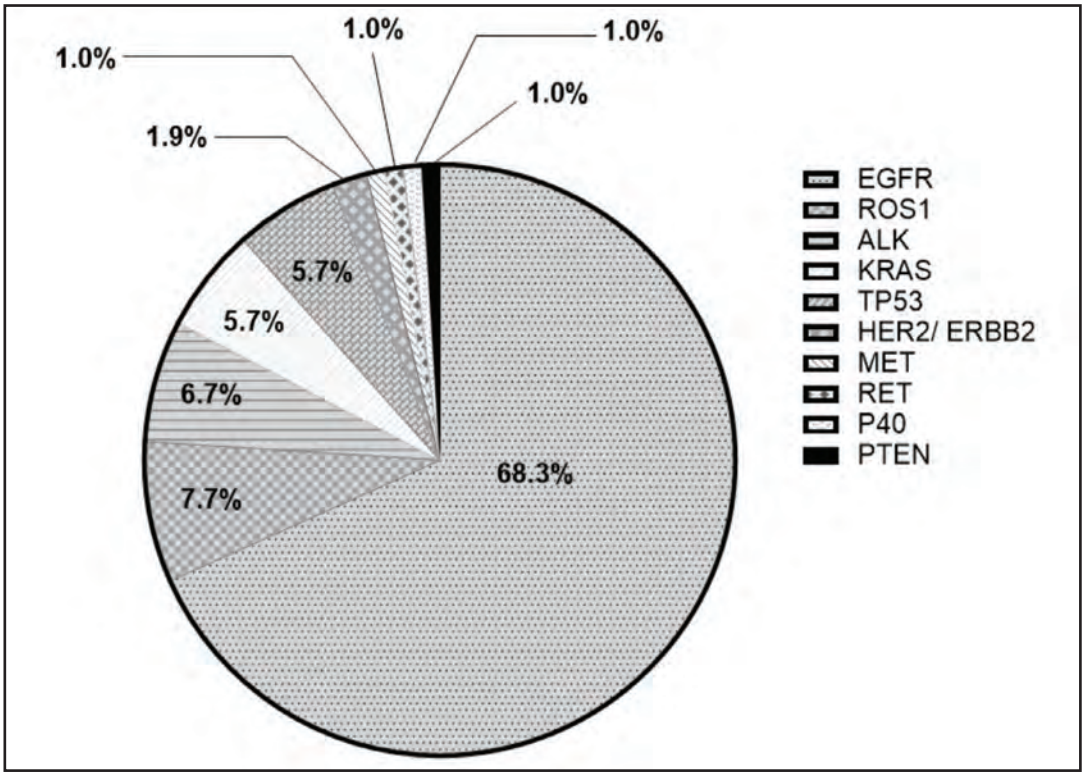

Fig. 1: B) Proportion of single gene mutations in early-stage, resectable NSCLC patients. The pie chart shows the percentage distribution of types of single-gene mutations in the patients.

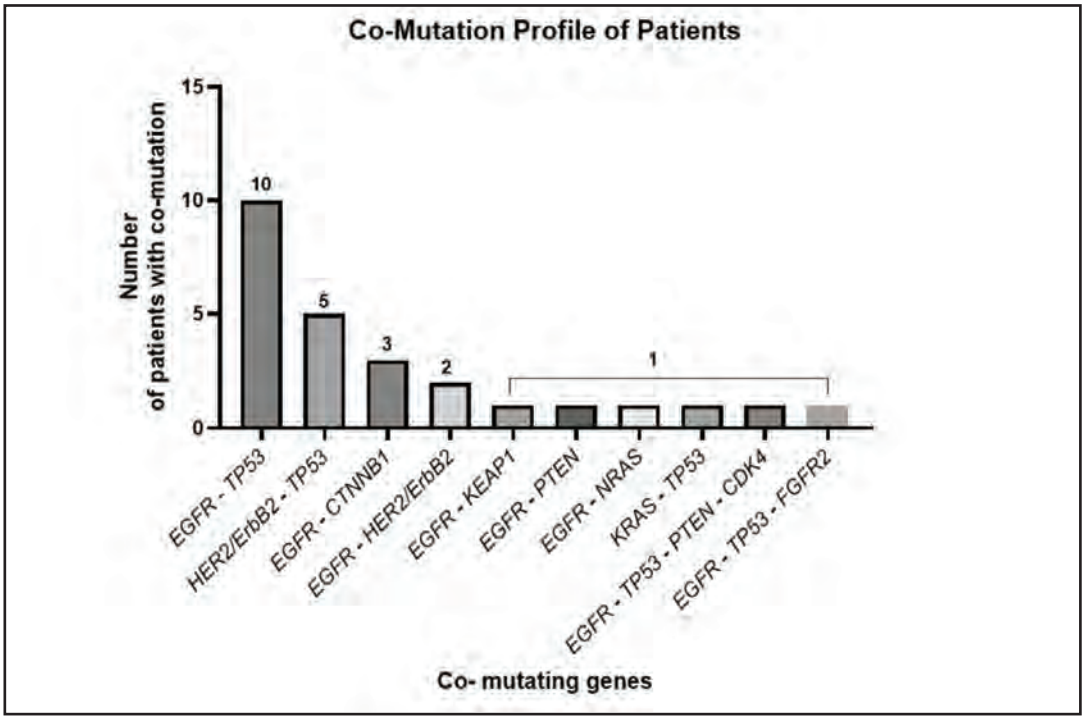

Fig. 2: A) Frequency of co-mutations in early-stage, resectable NSCLC patients. Each bar represents the number of patients with co-mutating genes, ranging from two to four.

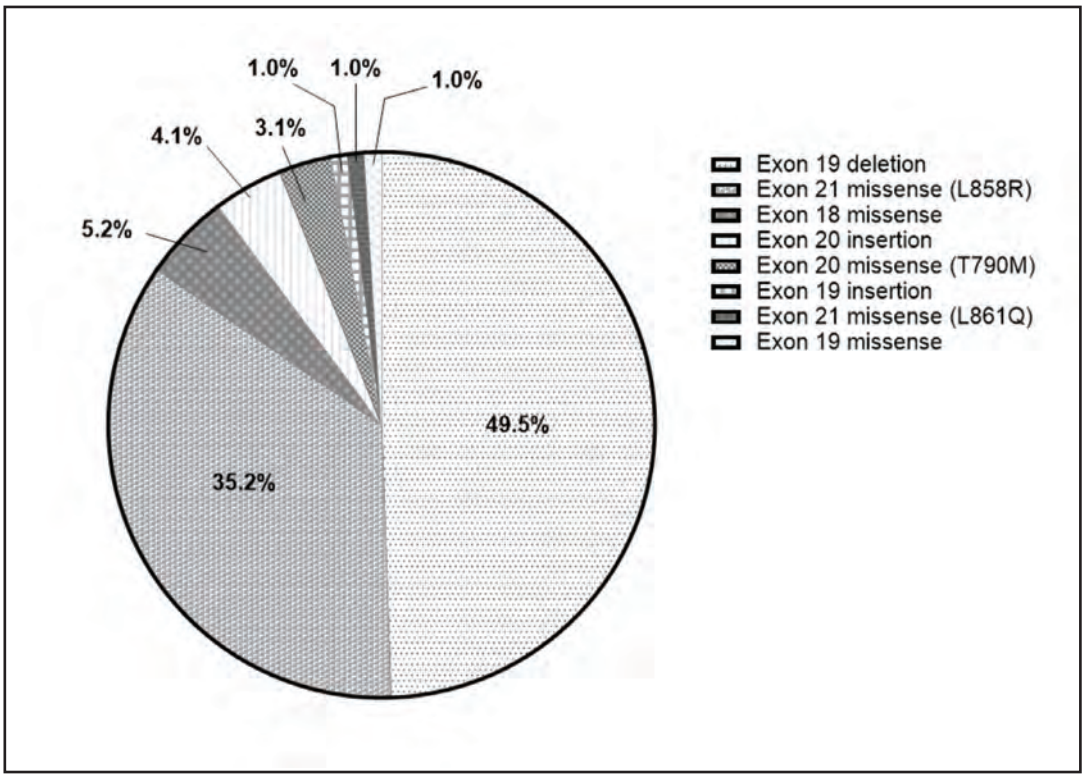

Fig. 2: B) Frequency of EGFR gene mutation subtypes in early-stage, resectable NSCLC patients. The pie chart shows the percentage distribution of subtypes of EGFR gene mutation in the patients.

appropriate biomarker-guided therapy. Pathologists should be empowered to initiate testing independently, ideally using NGS. Recently published clinical practice guidelines for early-stage NSCLC in Malaysia strongly encourage genomic molecular profiling as a reflex testing, at the start of the patient journey, where feasible, for stage IIA-IIIB-N2 NSCLC.[13] However, testing costs and variable insurance coverage remain barriers, highlighting the importance of informed consent and transparent discussions about potential out-of-pocket expenses.

Advances in adjuvant EGFR-TKI therapy and the role of mutation subtypes

The development of EGFR-TKIs has fundamentally transformed the management of EGFR-mutant NSCLC. The most important predictor of therapeutic benefit with TKI therapy is the EGFR mutation subtype. Osimertinib, a third-generation oral EGFR-TKI, is the current standard of care for EGFR-TKI sensitising (exon 19 deletion and L858R exon 21 missense) mutations. The ADAURA trial established osimertinib as a transformative adjuvant therapy, demonstrating significant DFS and OS improvements, including a 51% reduction in death risk at five years, following curative surgery.[14,15] In our study, 40/55 (72.7%) of eligible patients (stage 1B and above) received osimertinib (data not shown). Ongoing studies such as NeoADAURA,[16,17] ADAURA-2,[18] and TARGET[19] will further clarify the role of neoadjuvant and extended adjuvant EGFR-TKI therapy across disease stages.

In this study, NGS testing revealed that 84.6% of patients with EGFR-mutant NSCLC harboured sensitising mutations amenable to osimertinib treatment. This high prevalence highlights the importance of comprehensive molecular testing and profiling, locally, to guide appropriate biomarker-driven therapy. However, despite all our patients receiving an oncology review post-surgery, 27% of eligible patients did not receive Osimertinib (data not shown), suggesting cost and accessibility to therapy remain a real-world impediment even in an urban, private setting.

Identification of other mutations in NSCLC patients

Beyond EGFR, TP53, HER2/ErbB2, ROS1 and ALK were among the genetic mutations detected in our study population, either as a single mutation or a co-mutation. The most prevalent co-mutation in our EGFR-positive patients involved the TP53 gene, observed in 10 out of 20 patients with tumours that harboured co-mutations (50%). EGFR-mutant tumours with a TP53 co-mutation generally have a worse OS compared to wild-type TP53 patients receiving targeted therapy.[20]

While not all TP53 mutations are associated with a poorer prognosis, missense mutations, particularly on exon 8, have been shown to carry a worse progression-free survival (PFS), including those who developed T790M resistance mutations following treatment with osimertinib.[21,22] EGFR-mutant lung adenocarcinoma patients with TP53 co-mutation also had a higher tumour mutational burden and a worse recurrence-free survival compared to patients with only EGFR mutations.[23] Additionally, the presence of co-mutations of TP53 as well as other tumour suppressor genes such as RB1, NF1, ARID1A, BRCA1, and PTEN in patients with metastatic EGFR-mutant NSCLC has been associated with poor outcomes and reduced response when given EGFR TKIs.[24] Hence, such patients may potentially benefit from adjuvant chemotherapy in addition to TKI therapy and require closer follow-up as well as a low threshold for early re-biopsy in cases of suspected relapse.

HER2/ErbB2 mutations reported in 1-6% of NSCLC tumours often involve insertions in exon 20 of HER2/ErbB2 gene and are more common in female non-smokers. Our study findings (6.1%) align with this, where all but one patient with a HER2/ErbB2-mutated tumour harboured an exon 20 insertion or duplication. This is similar to another regional study that focused on Asians with non-squamous NSCLC.[25] Interestingly, five of our seven HER2/ErbB2 mutant patients also harboured a TP53 co-mutation, while two had concomitant EGFR mutations (Figure 3). Co-mutations of TP53 and HER2 are associated with a higher incidence of brain metastases in NSCLC patients, and shorter PFS and OS. Patients with these co-mutations also have a poorer response to targeted therapy.[26] In HER2-mutant lung cancers, TP53 is the most common co-mutation, whereas co-mutations of EGFR and HER2 are extremely rare. The existence of co-mutations may confer treatment resistance, which emerging treatments seek to surmount.

ROS proto-oncogene 1 (ROS1) rearrangements have been identified in 1- 2.6% of NSCLC patients and are sensitive to TKIs such as crizotinib, an approved first-line targeted therapy. ROS1 rearrangements are more commonly found in adenocarcinomas with distinct histological characteristics, women, young patients and light- or never-smokers.[27,28] The high frequency of ROS1 positivity (5.5%) we observed may be attributed to the predominance of female never-smokers with adenocarcinoma in our patient population.

Anaplastic lymphoma kinase (ALK) rearrangements were detected in approximately 5% of our patients, consistent with global estimates.[12] ALK-positive NSCLC patients tend to be younger, non-smokers, and present with predominantly adenocarcinoma.[29] Our ALK patients were slightly younger (mean 50.6 years), all non-smokers with more advanced disease (data not shown). Four of our seven patients commenced maintenance adjuvant alectinib (a second-generation ALK inhibitor). A recent phase III RCT (ALINA study) demonstrated significantly better DFS (88.3% (TKI) versus 53.3% platinum-based chemotherapy (PBC) at three years in fully resected ALK+ (stage II-IIIA) patients who received adjuvant alectinib 600mg twice daily for two years compared with PBC.[30] Patients who received alectinib in lieu of chemotherapy had a 76% reduction in the risk of disease recurrence. A similar DFS benefit was observed in the 'intention to treat' group, which included stage IB disease, driven by a better CNS disease-free survival (HR 0.22). Currently, OS data remains immature. These findings suggest that all resected IB-IIIA ALK-positive patients should be offered adjuvant alectinib for a minimum of two years. Meanwhile, the ongoing NAUTIKA1[31] and NEOLORA[32] trials studying neoadjuvant alectinib and lorlatinib (a third-generation ALK inhibitor), respectively, in stage IB-IIIB ALK-rearranged NSCLC will inform on the potential benefit of

upfront treatment. This again highlights the importance of reflex molecular genomic testing for any newly diagnosed early-stage rNSCLC.

Other than the genes described, EGFR co-mutations were observed with CTNNB1, KEAP1 and PTEN. CTNNB1 mutation has been associated with poor recurrence-free survival in patients with EGFR-mutant lung adenocarcinoma.[33,34] Similarly, mutation in KEAP1 was associated with shorter DFS and a negative prognosticator for patients with advanced-stage tumours.[35] PTEN loss is another mutation associated with shorter PFS and OS.[36] All these genes are involved in the development of off-target resistance to osimertinib and in such patients, a more cautious approach is required.

PD-L1 expression and challenges with predictive biomarkers

We did not observe any correlation between PD-L1 expression and EGFR mutation status, similar to the findings from the EARLY-EGFR study.[11] PD-L1 expression is part of a complex dynamic tumour microenvironment, and intra-tumoural heterogeneity further complicates interpretation: in our small sample of paired biopsies, discordance was observed in 83% of cases (data not shown). This variability limits the predictive utility of PD-L1 expression for therapeutic response to ICI therapy. Complementary biomarkers, such as circulating tumour DNA (ctDNA), may help refine patient selection, including safe adjuvant therapy de-escalation in appropriate patients, thereby mitigating unnecessary toxicity and costs.

Financial toxicity and access to targeted therapy

Affordability remains a critical barrier to treatment access. In the EARLY-EGFR study, only 8.2% of eligible patients received a TKI.[11] While a majority (73%) of our patients were able to start osimertinib, this likely reflects our private urban practice. A lower compliance with standard-of-care adjuvant osimertinib can be expected in non-private and rural settings. Nationally, financial hardship is common, with over half of Malaysian households reporting catastrophic expenditure within a year of a cancer diagnosis.[37] Ensuring equitable access to effective but high-cost targeted therapies must be a healthcare priority. Despite being an approved first-line therapy since 2018, many Malaysians with advanced EGFR-mutant NSCLC still have poor access to osimertinib and are instead prescribed more affordable first and second-generation EGFR-TKIs.[38] Patients who progressed often still did not have access to osimertinib and were offered chemotherapy. This lack of accessibility impacts their time on treatment and overall prognosis.

Implications for Contemporary Clinical Practice

Our findings support routine reflex genomic profiling in all non-squamous NSCLC upon diagnosis, including for early-stage resectable disease. Timely identification of actionable mutations will inform optimal treatment strategies, including adjuvant TKI use and neoadjuvant ICI use for non-oncogene-driven stage-dependent NSCLC, pre-operatively. Additionally, reliance solely on a tobacco history will overlook a substantial proportion of early-stage lung cancer in asymptomatic never-smokers, underscoring the need to broaden screening criteria with emphasis on a salient family history for the disease. Cost remains a real-world impediment and precludes many eligible patients from proven standard-of-care adjuvant therapy. Future healthcare financing strategies must ensure that highly efficacious drugs are affordable and accessible.

LIMITATIONS

This was a contemporary but small retrospective observational study from a private urban setting with a predominantly Chinese, female, non-smoking population. Therefore, our findings may not be generalizable to the wider Malaysian population. Larger, multicentre studies involving more diverse groups of patients are needed to validate these findings and establish true national genomic prevalence patterns.

CONCLUSION

Our study highlights the high prevalence of actionable EGFR mutations in early-stage Malaysian NSCLC patients. Reflex genomic testing at the start of the patient journey and equitable access to targeted therapies are critical to improving outcomes. Future work should focus on broader screening strategies including targeting high-risk non-smokers, better funding mechanisms, and the integration of novel biomarkers into routine care.

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ETHICS DECLARATIONS

Conflict of Interest Disclosures

Professor A. Sachithanandan is on the thoracic advisory board for AstraZeneca, Bristol Myers Squibb, Roche, and Merck Sharp & Dohme. Professor R. Pathmanathan is on the advisory board of several pharmaceutical (Merck Sharp & Dohme, AstraZeneca, Roche) and laboratory equipment manufacturers (ThermoFisher, Agilent, Roche, BioRad). The remaining authors have no disclosures or conflicts of interest.

ETHICAL APPROVAL

This study was approved by the respective Independent Research Ethics Committees of Sunway Medical Centre and Subang Jaya Medical Centre, which waived the requirement for informed consent owing to the retrospective nature of the study. This research was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments or comparable ethical standards.

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ORIGINAL ARTICLE

Clinical characteristics and factors affecting visual outcomes in patients with herpes simplex keratitis: A tertiary hospital experience

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ABSTRACT

Introduction: Herpes Simplex Keratitis (HSK) is a leading cause of infectious corneal blindness globally. However, clinical data and visual outcomes specific to the Malaysian population are limited. This study aimed to identify common clinical features, visual outcome and its associated factors in patients treated at a Malaysian tertiary hospital.

Materials and Methods: A retrospective cohort study was conducted at Hospital Pakar Universiti Sains Malaysia (HPUSM) between June 2013 and June 2024. Medical records of patients diagnosed with HSK and followed for at least six months were reviewed. Sixty-seven patients were included. Data collected included demographics, presenting symptoms, best-corrected visual acuity (BCVA) at presentation and after treatment, ocular findings, subtype of HSK and complications. Statistical analyses were performed using SPSS version 28.0. Paired t-tests was used to analyse changes in BCVA and multiple linear regression was performed to identify factors associated with final visual outcome.

Results: The mean age at presentation was 50.42±17.19 years with a slight male predominance (52.2%). Most cases were unilateral (91.1%). Common presenting symptoms were reduced vision (89.6%) and eye redness (85.1%). Keratouveitis was the most frequent subtype (37.3%). Complications included corneal scarring (73.1%), recurrence (49.3%) and glaucoma (11.9%). BCVA significantly improved post-treatment (p<0.001). Older age, central corneal involvement, elevated intraocular pressure at presentation, and stromal vascularisation were significantly associated with poorer visual outcomes.

Conclusion: This study outlines the clinical spectrum and visual outcomes of HSK at a tertiary hospital in Malaysia and identifying several predictive factors for poor vision. These findings may aid clinicians in risk stratification and optimising management strategies.

KEYWORDS:
Herpes simplex virus, herpes simplex keratitis, risk factors, visual outcome

INTRODUCTION

Herpes Simplex Keratitis (HSK) is a major cause of infectious corneal blindness worldwide and is caused by the Herpes Simplex Virus (HSV).[1] The incidence of Herpes Simplex Keratitis (HSK) was 1.7 million in 2016 globally per year.[2]

In Malaysia, HSK remains a significant public health concern. However, detailed data on its clinical characteristics, visual outcomes and associated prognostic factors are still limited.[3] In addition, there are no published studies that specifically evaluate the factors associated with visual outcomes of HSK within the Malaysian population. Identifying these factors is essential for improving clinical decision-making and patient management in local settings.

Therefore, this study aimed to address this gap by analysing the clinical features and determining the factors associated with visual outcomes in patients with HSK treated at a tertiary hospital in Malaysia.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Ophthalmology Clinic, HPUSM from June 2013 to June 2024. Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/KK/25010124) and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

All patients aged over 18 years who were diagnosed based on typical cornea signs of HSK such as a classical dendritic pattern on epithelium, stromal infiltrate/ opacification with or without ulceration, presence of fine keratic precipitates and presence of anterior chamber inflammation with decreased or absent corneal sensation, were selected. Patient who had a minimum follow-up of six months were included. Patients who presented with recurrent infection at their initial visit or those who were undergoing treatment were excluded. For bilateral cases, the eye with better visual acuity was excluded from analysis to avoid confounding, similar to the study done by Cabrera-Aguas et al.[10] Patients with other ocular conditions that may affect the visual outcome such as cataracts, iritis, glaucoma and other eye diseases were also excluded (Figure 1).

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Demographic and clinical data were obtained from medical records, including age, sex, race, occupation and comorbidities. Presenting symptoms and BCVA at the first visit were recorded. Slit-lamp examination findings were documented for further subtypes classification. The clinical classification of HSV keratitis was based on the corneal site and anatomical localisation. Central involvement was considered if central 4-mm optical zone was involved. In this study, we used the following classification:[1] 1) Epithelial keratitis: a) dendritic epithelial ulcers (lesions with branching, linear pattern with terminal bulbs), and b) geographic epithelial ulcers (broad ulcers with swollen, scalloped, or geographic epithelial borders); 2) Stromal keratitis: a) stromal keratitis without ulceration (non-necrotizing, interstitial, or immune stromal), and b) stromal keratitis with ulceration (necrotizing); and 3) endothelial keratitis or endotheliitis (disciform).[1] Characteristic findings of herpetic keratouveitis included herpetic keratitis, elevated intraocular pressure (IOP) >21mmHg, keratic precipitates (KPs) and iris atrophy.[14] In addition, the location and associated features were also documented.

In this study, we followed the HSV keratitis treatment guidelines reviewed and accepted by the Hoskins Center for Quality Eye Care, American Academy of Ophthalmology, in the June 2014 Compendium of Evidence-Based Eye Care.[13] The antiviral agents used were topical acyclovir 3% and oral acyclovir 400mg or 800mg based on the clinical presentation, following the guideline. Topical prednisolone acetate 1% was used in cases requiring topical steroids. Oral acyclovir 400mg twice daily was given as prophylaxis for patients with stromal keratitis and for patients with multiple recurrences of any type of HSK. For patients who presented with high IOP, IOP-lowering agents like topical timolol 0.5%, topical dorzolamide 2% and topical brimonidine 0.15% were given. Patients were regularly re-examined after the initiation of treatment and assessed for treatment-related local or systemic adverse reactions. BCVA and the presence of corneal neovascularisation or haze were recorded after treatment completion. Any new symptomatic episode with typical findings of HSK following resolution of the previous episode was considered recurrence, regardless of duration from onset.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Corp., Armonk, NY). A paired t-test was used to compare the mean BCVA at presentation and after treatment at the last follow-up. Simple linear regression analysis was done first, and the factors with a p-value <0.25 and factors that were found to be significant from the previous studies were used for multiple linear regression. Multiple linear regression was employed to identify factors associated with poor final visual outcomes. A p-value of < 0.05 was considered statistically significant. The significant factors were further analysed to report adjusted R^2 and to assess multicollinearity.

RESULTS

A total of 67 patients were included in the study. The mean follow-up duration was 24.49±22.72 months. The mean age at presentation was 50.42±17.19 years. There was a slight male predominance (52.2%), and most patients were of Malay ethnicity (91.0%). Comorbidities were observed in 41.8% of patients, with cardiovascular disease (20.9%) and combined diabetes and cardiovascular disease (14.9%) being the most common (Table I).

Unilateral involvement was seen in 91.1% of cases. The most frequently reported symptoms were reduced vision (89.6%) and eye redness (85.1%), followed by eye pain (50.7%) and eye discharge (41.8%). Keratouveitis was the most common clinical subtype (37.3%), followed by stromal keratitis (32.8%) (Table I).

Reduced corneal sensation was observed in 68.7% of eyes, while stromal vascularisation and Descemet striae were each noted in 25.4% of cases. Central and paracentral corneal involvement were nearly equally distributed. The most frequent complications were corneal scarring (73.1%), which was observed in all subtypes and recurrence (49.3%), while glaucoma was present in 11.9% of cases (Table I).

Comparison of BCVA before and after treatment revealed a statistically significant improvement. The mean BCVA at presentation was 0.81±0.75 logMAR, which improved to 0.44±0.70 logMAR at the final follow-up visit. The mean difference was 0.37 logMAR (95% CI: 0.18 to 0.55; p<0.001), indicating a significant gain in visual acuity following treatment (Table II).

Simple linear regression analysis was conducted to assess the association between various clinical variables and final visual acuity. Factors found to be significant were included in a multiple linear regression model. In the final model, four variables were significantly associated with poorer visual outcomes: increasing age (adjusted β=0.02; 95% CI: 0.01, 0.03; p<0.001), central corneal involvement (adjusted β=0.29; 95% CI: 0.02. 0.56; p=0.039), elevated intraocular pressure (IOP) at presentation (adjusted β=0.71; 95% CI: 0.31. 1.12; p<0.001) and presence of stromal vascularisation (adjusted β=0.45; 95% CI: 0.13, 0.76; p=0.006) (Table III).

The final regression model, including IOP, age, stromal vascularisation and central corneal involvement, explained 40.5% of variability in the outcome. Each variable added improved the model, indicating these factors are independently associated with the dependent variable. The strongest additional predictor was age, followed by IOP, then stromal vascularisation and lastly central corneal involvement. There was no multicollinearity (VIF<5), confirming that each predictor contributed uniquely to the final model.

Gender, keratitis subtype, comorbidities (diabetes and cardiovascular disease), reduced corneal sensation, corneal scarring, and recurrence were not significantly associated with post-treatment visual outcomes in this cohort (Table III).

DISCUSSION

HSK is a significant cause of corneal blindness and is a considerable public health challenge worldwide, including Malaysia.[2,3] Detailed epidemiological data and clinical outcomes specific to the Malaysian population remain

Table I: Demographic and Clinical Characteristics of Patients with HSK

Variables	n (%)
Age in years, mean±SD	50.42±17.19
Gender	
Male	35 (52.2)
Female	32 (47.8)
Race	
Malay	61 (91.0)
Chinese	5 (7.5)
Siamese1 (1.5)	
Co-morbidities	
Diabetes Mellitus	14 (20.9)
Cardiovascular Disease	10 (14.9)
Both DM and CVD	39 (58.2)
Others	2 (3.0)
Laterality	
Right	28 (41.8)
Left	33 (49.3)
Bilateral	6 (9.0)
Presenting symptoms	
Eye redness	57 (85.1)
Eye discharge	28 (41.8)
Eye pain	34 (50.7)
Eye discomfort	30 (44.8)
Foreign body sensation	28 (41.8)
Photophobia	25 (37.3)
Reduced vision	60 (89.6)
HSK subtype	
Epithelial keratitis	9 (13.4)
Stromal keratitis	22 (32.8)
Endotheliitis	11 (16.4)
Keratouveitis	25 (37.3)
Associated features	
Corneal oedema	33 (49.3)
Immune Weisley ring	0 (0.0)
Reduced corneal sensation	46 (68.7)
Stromal vascularisation	17 (25.4)
Descemet striae	17 (25.4)
Hypopyon	1 (1.5)
Site of keratitis	
Central	31 (46.3)
Paracentral	32 (47.8)
Peripheral	4 (6.0)
Complications	
Recurrence	33 (49.3)
Corneal scarring	49 (73.1)
Glaucoma	8 (11.9)
Endophthalmitis	1 (1.5)
Corneal perforation	1 (1.5)

Abbreviations: SD: Standard deviation

Table II: Comparison of mean BCVA at presentation and post-treatment

Variables	At presentation (Mean ± SD)	After treatment (Mean ± SD)	MD (95%CI)	p-value
BCVA (logMAR)	0.81±0.75	0.44±0.70	0.37 (0.18, 0.55)	<0.001

Abbreviations: SD: Standard deviation, MD: Mean difference, CI: Confidence interval, BCVA: Best corrected visual acuity, logMAR: Logarithm of the Minimum Angle of Resolution

limited, and, to the best of our knowledge, the factors associated with the visual outcome of HSV among the Malaysian population remain unexplored. In our study, we analysed 67 patients with HSK over an 11-year period, aiming to explore the clinical spectrum, complications and prognostic factors associated with visual outcomes in a Malaysian tertiary hospital setting.

The mean age of presentation was 50.4 years, notably higher than that reported in earlier Malaysian studies (36.2 years)[3] This may reflect changing demographics and improved access to healthcare for older populations. A slight male predominance was observed, aligning with global patterns,[4] though differing from local data where equal gender distribution was previously reported.[3]

Table III: Factors Associated with Visual Outcome in HSK

Factors	Simple linear regression		Multiple linear regression	
	Crude b (95% CI)	p-value	Adjusted b (95% CI)	p-value
Age	0.02 (0.01, 0.03)	<0.001	0.02 (0.01, 0.03)	<0.001
Female	-0.28 (-0.61, 0.07)	0.111	-	-
Cardiovascular and DM	0.36 (-0.11, 0.84)	0.132	-	-
Keratitis subtype				
Stromal	0.02 (-0.35, 0.39)	0.909	-	-
Endothelial	-0.09 (-0.56, 0.38)	0.696	-	-
Keratouveitis	0.13 (-0.22, 0.49)	0.457	-	-
Corneal involvement				
Central	0.31 (-0.03, 0.65)	0.073	0.29 (0.02, 0.56)	0.039
Paracentral	-0.22 (-0.56, 0.12)	0.202	-	-
Ocular co-morbid	0.27 (-0.10, 0.64)	0.151	-	-
Associated ocular features				
Corneal oedema	0.27 (-0.07, 0.61)	0.113	-	-
High IOP	0.97 (0.52, 1.42)	<0.001	0.71 (0.31, 1.12)	<0.001
Reduced corneal sensation	-0.22 (-0.59, 0.15)	0.241	-	-
Stromal vascularisation	0.47 (0.09, 0.85)	0.017	0.45 (0.13, 0.76)	0.006
Descemet striae	0.16 (-0.24, 0.55)	0.426	-	-
Complications:				
Glaucoma	0.62 (0.11, 1.13)	0.018	-	-
Recurrence	-0.08 (-0.43, 0.27)	0.648	-	-
Corneal scarring	0.18 (-0.21, 0.56)	0.366	-	-
Antiviral prophylaxis	0.12 (-0.33, 0.57)	0.596	-	-

Abbreviations: CI: Confidence interval, IOP: Intraocular pressure, DM: Diabetes mellitus

Table IV: Comparison of factors associated with visual outcomes in previously published studies

Authors	Country	Year published	Sample size	Factors associated with visual outcome
Rosenberg et al.[9]	USA	2020	104	Older age, DM, surgeries, scarring, glaucoma, recurrence
Cabrera-Aguas et al.[10]	Australia	2021	296	Recurrence, keratouveitis, scarring
Lotfi et al.[11]	Kuwait	2023	72	Corneal haze
Zhang et al.[12]	China	2024	198	Age ≥ 65, prolonged disease, epithelial/stromal type

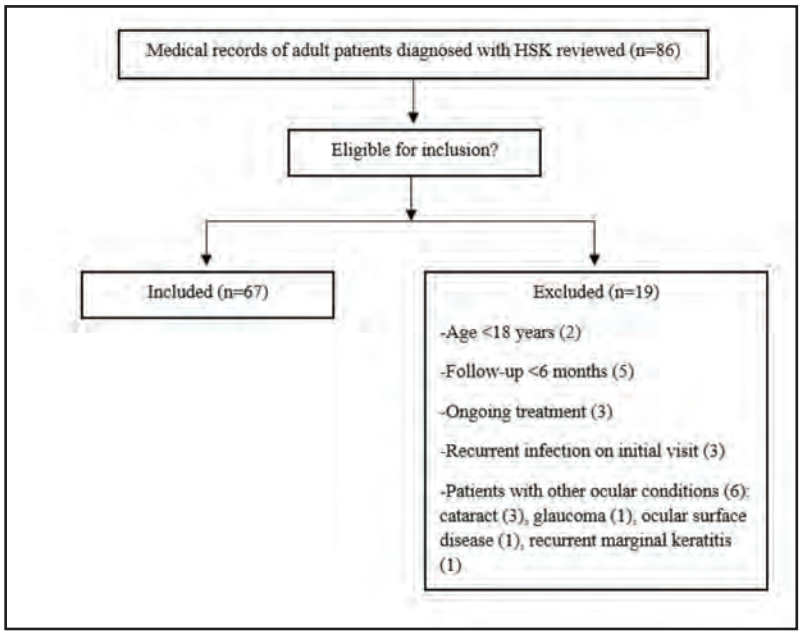

Fig. 1: Sample derivation

The most common presenting symptoms were reduced vision and eye redness, followed by pain, discomfort, photophobia, and foreign body sensation. Similar symptoms were reported in studies from Malaysia and Korea.[3,4] Reduced corneal sensation was present in 68.7% of cases, a well-recognised clinical sign of herpetic keratitis, corroborating the findings of Danileviciene et al.[5] A previous study done in Malaysia found 75.0% cases with reduced corneal sensation. It is important to note that corneal sensation was assessed with the cotton wisp test, and quantitative assessment was not done in our study, and this may introduce bias. Other associated findings of stromal vascularisation observed by Rodriguez-Garcia et al.,[6] was also present in our patients.

The distribution of HSK subtypes revealed keratouveitis as the most frequent, followed by stromal keratitis, endotheliitis and epithelial keratitis. These findings contrast with reports from Korea, Australia and China where epithelial keratitis was more common.[4,10,12] This discrepancy could be due to our centre being a tertiary referral hospital, hence likely to manage more severe cases. Milder epithelial cases might be treated at primary care level and not referred. Ethnic and genetic variations could also contribute to these differences.

Complications were common, with corneal scarring affecting the majority of patients (73.2%), followed by recurrence and glaucoma. Other studies reported recurrence of HSK as the main complication.[2,7,9] Recurrence was noted in 49.3% in our study, whereas it was 36.4% in the previous study done in Malaysia.[3] This difference in recurrent rates may be attributed to longer duration of study and a greater number of patients included in the current study compared to the previous study. Additionally, demographic changes like an older mean age may have contributed to the higher recurrent rates. Rare cases of endophthalmitis and corneal perforation were also observed. These findings are consistent with previous studies reporting high recurrence and complication rates in HSK.[2,7-9] Furthermore, corneal scarring and recurrence remain the primary causes of long-term visual impairment. This underscores the need for improved training and awareness among healthcare providers regarding the clinical signs of HSK, enabling early diagnosis and timely management.

There was significant improvement in the visual acuity from initial presentation and post- treatment, highlighting the effectiveness of medical and supportive interventions. However, the extent of visual recovery varied depending on disease severity and complications. This suggests that current treatment protocols should be reinforced and possibly expanded to include more aggressive management approaches for patients presenting with severe symptoms, high IOP or complications.

Age of the patient, central corneal involvement, presence of stromal vascularization and high IOP at presentation are the statistically significant factors associated with the final visual acuity. Our findings are in line with Rosenberg et al., who found older age, scarring, glaucoma, and recurrent disease as predictors of poor outcomes.[9] Cabrera-Aguas et al.,[10] also highlighted keratouveitis, recurrence, and scarring as significant prognostic factors. The differences and similarities across studies underscore the multifactorial nature of HSK outcomes and the importance of localised data to guide clinical decisions. Increasing age has been consistently associated with worse visual prognosis, possibly due to delayed healing and pre-existing ocular comorbidities.[9,12] Central corneal involvement directly affects the visual axis, thus compromising visual recovery. Elevated IOP, likely due to herpetic trabeculitis or steroid-induced glaucoma, can also impair visual outcomes. Stromal vascularisation reflects chronic inflammation and scarring, leading to corneal opacity.[6,10] Hence, monitoring and control of IOP needs to be prioritised, and close monitoring is critical in patients presenting with the risk factors.

Interestingly, factors such as gender, coexisting diabetes or cardiovascular disease and keratitis subtype were not statistically significant predictors in our model. A summary of previously published studies and their associated visual outcome predictors is provided in Table IV.[9-12] While other studies found recurrence, scarring, and diabetes mellitus to be significant factors,[9-11] these were not statistically significant in our cohort. This could be due to variability in our presentation, with keratouveitis being the most common presentation compared to other studies.

This retrospective study from a single centre relied on clinical diagnosis without standardised laboratory confirmation, which may introduce bias. These factors limit internal validity and highlight the need for prospective multicentre studies with standardised diagnostic investigations.

CONCLUSION

Recognition of clinical patterns is crucial for early diagnosis and management of HSK. Visual outcomes were influenced by patient age, site of corneal involvement, IOP and stromal vascularisation. These findings provide a basis for improved local management strategies and may inform national clinical guidelines.

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ORIGINAL ARTICLE

A Malaysian study on COVID-19 (SARS-CoV-2) vaccination immune response in haemodialysis patients: A prospective, multicentre, cohort study

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ABSTRACT

Introduction: Patients with end-stage renal disease (ESRD) have compromised immune systems, possibly reducing their vaccine-induced antibody responses compared to the general population. COVID-19 remains a persistent threat, with the virus continuing to mutate into new variants. Similar to influenza, there is a possibility that COVID-19 could resurge significantly, underscoring the importance of understanding vaccine-induced immunity in vulnerable populations. This study aims to determine the immunogenicity of this group to the COVID-19 vaccine.

Materials and Methods: Haemodialysis patients receiving the Pfizer-BioNTech mRNA vaccine were followed for at least 13 months. Blood samples were collected prior to every vaccine dose and at multiple intervals thereafter. Neutralising antibodies (nAb) against SARS-CoV-2 were measured. Patients voluntarily reported any COVID-19 infection.

Results: Between April 2021 and January 2023, 271 patients received at least one dose of the vaccine; 212 of these had at least one blood sample tested for nAb. Booster doses were given 26.2 weeks after the second dose. nAbs were detected in 16.8% of patients before vaccination. The nAb levels were higher than the non-convalescent patients after the first dose, but it was not statistically significant. Breakthrough infections were self-reported in 29.3% of patients. A significant association between breakthrough infections and history of COVID-19 infection cannot be established (p=0.188). There were 34 deaths (16.0%); 2 related to COVID-19. Younger age was associated with higher nAb reactivity post-first dose, but this difference diminished after the second dose.

Conclusion: Almost complete seropositivity (98.4%) was achieved after two doses of vaccine. Sustained antibody levels after the third dose suggest the value of a booster dose in protecting this vulnerable population. However, the occurrence of breakthrough infections highlights the need for continued monitoring, preventive measures, and further research to optimise vaccination strategies in haemodialysis patients.

KEYWORDS:
COVID-19 vaccine, haemodialysis, end-stage renal disease (ESRD)

INTRODUCTION

As of 2024, the WHO has reported over 700 million COVID-19 cases globally. In Malaysia, there have been more than 5 million cases, resulting in over 30,000 deaths.[1] The rise in hospitalisations and mortality has added a significant burden to the healthcare system. In the latest report, more than 50,000 individuals with end-stage renal disease (ESRD) in Malaysia were on dialysis in 2022.[2] The COVID-19 pandemic has significantly impacted this population, who are at a higher risk of infection compared to healthy individuals due to their compromised immune systems. COVID-19 remains a persistent threat, with the virus continuing to mutate into new variants. Similar to influenza, there is a possibility that COVID-19 could resurge significantly, underscoring the importance of understanding vaccine-induced immunity in vulnerable populations.

The lack of vitamin D and erythropoietin and accumulation of uremic toxins in ESRD patients affect the immune function of these patients. On top of that, the main receptor of SARS-CoV-2, the angiotensin converting enzyme 2 (ACE 2), is highly expressed in the kidney. All these conditions can induce cytokine storms, inflammation and oxidative stress, and in return, further damaging the kidney and worsening the severity of the infection.[3] The overall estimated case fatality rate of COVID-19 in ESRD patients undergoing renal replacement therapy was 18.06%, significantly higher than the global average of 4.98%.[4]

Vaccine development began in 2020 with the goal of preventing and reducing the morbidity and mortality caused by COVID-19. In December 2020, the FDA granted the first Emergency Use Authorisation (EUA) for a vaccine designed to

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prevent COVID-19.[5] Currently, there are two mRNA vaccines that encode the SARS-CoV-2 spike protein-Pfizer-BioNTech and Moderna. In Malaysia, haemodialysis patients received the Pfizer-BioNTech vaccine. Research indicates that two doses of the Pfizer-BioNTech vaccine are 94-95% effective in preventing confirmed COVID-19 cases and 75% effective in preventing severe COVID-19 in the general population.[6,7]

However, the effectiveness of the vaccine can differ based on various factors such as age, comorbidities, and immune status. In ESRD patients, the efficacy of the vaccine further depends on factors such as lack of vitamin D and erythropoietin, uremic conditions and use of immunosuppressants.[3] Seroconversion rates and antibody titres have been found to be significantly lower in ESRD patients, whether on dialysis or not, compared with healthy individuals.[8-11] Nevertheless, in haemodialysis patients, one dose of vaccine can reduce the risk of infection and serious outcomes by 41% and 46%, respectively, while two doses can bring these numbers to 69% and 83%.[3]

The Centers for Disease Control and Prevention (CDC) recommends that individuals who are severely or moderately immunocompromised should receive two or three doses of the same brand of COVID-19 vaccine.[12] They may also be eligible for additional doses. The use of additional doses is to enhance immunity, extend the duration of protection, and improve their ability to produce sufficient immune responses. No specific COVID-19 vaccine is preferred over another.

This study was carried out after the COVID-19 vaccine became available in Malaysia in early 2021, with the aim to gather local data examining the immune response of mRNA COVID-19 vaccine in haemodialysis patients and hence, to guide our national COVID-19 vaccination plan for this specific population. We find that there is still a lack of evidence on the immunogenicity and breakthrough infections representing the Malaysian population. This study provides real-world data on the effectiveness of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine in haemodialysis patients from this region.

MATERIALS AND METHODS

This study was conducted in eight dialysis units across four states in Peninsula Malaysia. Patients on haemodialysis who participated in COVID-19 vaccination program were eligible to be enrolled in this study and were prospectively followed up for at least 13 months. All subjects received the Pfizer-BioNTech (BNT162b2) mRNA vaccine. Full COVID-19 vaccination was defined as two doses of the vaccine administered 3 weeks apart. Booster dose was optional and was administered at least six months after the second dose.

All blood samples (3 to 5 ml) were taken by trained healthcare personnel at each centre. Baseline blood sample was taken on the day before the first vaccination dose. Subsequent blood samples were taken again before the second dose and one, six and 12 months thereafter (Figure 1). Additional sampling points were drawn for those who took three doses of the vaccine. These blood samples were then sent to the laboratory to be spun at 1000 x G for 15 minutes in a refrigerated centrifuge at 20˚C and the sera aliquoted into cryotubes. The cryotubes were then stored in a -80˚C freezer before being sent to the Institute of Medical Research to be analysed.

All samples were tested for IgG antibody against SARS-CoV-2 spike protein (S1) receptor-binding domain (RBD) by trained personnel, using the ADVIA Centaur SARS-CoV-2 spike IgG assay, sCOVG (Siemens Healthcare Diagnostic, NY, USA). The sCOVG assay is a fully automated two-step sandwich immunoassay using indirect chemiluminescent technology for qualitative and quantitative detection of IgG, including neutralising antibodies (nAb). The assay outputs an sCOVG index value was standardised to the WHO International Standard for anti-SARS-CoV-2 Immunoglobulin unit BAU/ml using a conversion factor of 21.8.[13] The positive threshold was 21.8 BAU/ml.

COVID-19 status was voluntarily reported by the patients. Breakthrough infection was defined as a SARS-CoV-2 virus infection that occurred at least 14 days after the last COVID-19 vaccine dose.

Statistical analysis

Continuous variables were summarised as means and standard deviations while categorical variables were expressed as frequencies and percentages. Chi-squared test or Fisher's exact test was used to compare between groups. Analysis was performed using STATA 11. A p-value of <0.05 was considered statistically significant.

RESULTS

Between April 2021 and March 2022, 271 patients (52.0% males) with a mean (SD) age of 61.1 (14.4) years received at least two doses of the Pfizer-BioNTech (BNT162b2) mRNA vaccine.

Of these, 212 patients who had at least one blood sample tested for neutralising antibodies were included in the study. Characteristics of these patients are shown in Table I. Booster dose was administered on average 26.2 weeks after the second dose. Median interval time between the second and booster doses was 25.4 weeks. There were 19 deaths (9.0%), of which 2 (10.5%) were related to COVID-19.

Breakthrough infections occurred in 62 (29.3%) patients; 21 (33.9%) and 41 (66.1%) occurred after the second and third doses, respectively, with a median time of 14.3 weeks after the second dose and 16.6 weeks after the third. Overall, a median (IQR) time of 15.5 (13.7, 18.1) weeks elapsed between the last vaccination dose and breakthrough infection. Seven (11.3%) of these patients were convalescent patients. There was no association between history of COVID-19 infection and breakthrough infection (p=0.188).

Neutralising antibody response

At some timepoints, the number of samples may be less than the total number of patients as some samples were compromised, volume was too little, or sample was not taken. The number of samples analysed are stated in the denominator.

Table I: Characteristics of subjects, n = 212

Characteristics	
Mean age, years (SD)	59.7 (14.7)
Gender	
Male, n (%)	112 (52.8)
Female, n (%)	100 (47.2)
Ethnicity	
Malay, n (%)	99 (46.7)
Chinese, n (%)	90 (42.5)
Indian, n (%)	15 (7.1)
Others, n (%)	8 (3.8)
Total doses of COVID-19 vaccine received	
2 doses, n (%)	25 (11.8)
2 doses + booster, n (%)	187 (88.2)

Table II: Neutralising antibody reactivity after doses 1 and 2

	Prior COVID-19 infection		p-value2
	No	Yes	
3 weeks post Dose 1			
Non-reactive	70 (39.8%)	10 (29.4%)	0.255
Reactive[1]	106 (60.2%)	24 (70.6%)	
1 month post Dose 2			
Non-reactive	1 (0.7%)	2 (6.1%)	0.08
Reactive[1]	154 (99.4%)	31 (93.9%)	

[1]Reactive (or positive) is determined according to the neutralising antibody index value of ≥ 1.00 U/ml (21.8 BAU/ml)
[2]Chi-squared test or Fisher's Exact test

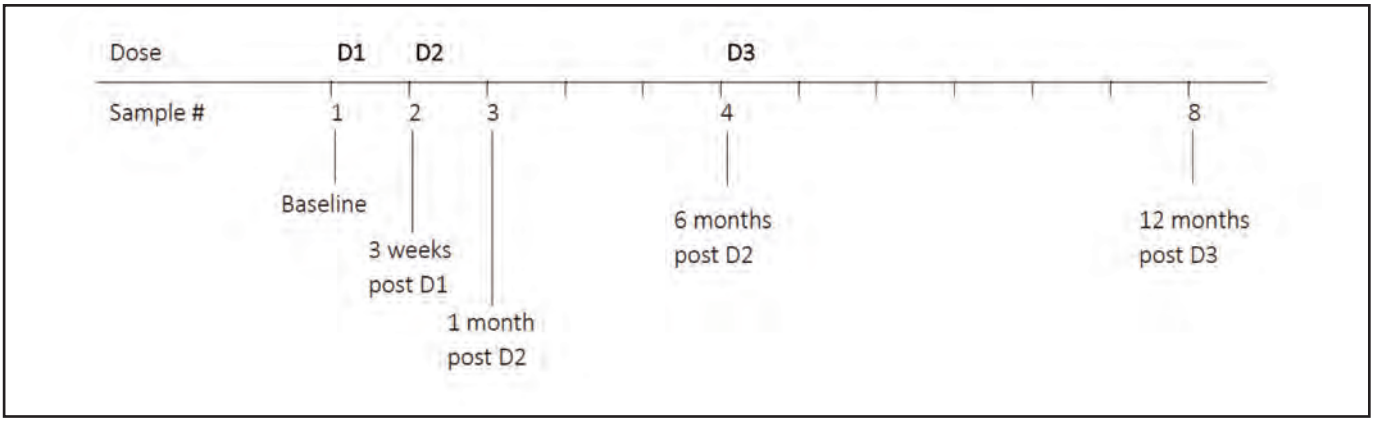

Fig. 1: Vaccination and blood sampling timeline

Neutralising antibodies against SARS-CoV-2 were detected in 16.8% (n=35/209) ESRD patients at baseline before their first vaccination dose, likely an indication of a recent or prior COVID-19 infection. The median (IQR) nAb titre among these convalescent individuals at baseline were 32.7 BAU/ml (24.6, 72.4) and ranged between 16.1 and 2180 BAU/ml, which was the upper limit of detection.

Neutralising antibodies were detected in 61.9% (n=130/210, median: 95.8 BAU/ml) and 98.4% (n=185/188, median: 2180 BAU/ml) patients after the first and second doses, respectively. The median nAb titres were higher three weeks after the first dose in patients previously exposed to COVID-19 infection (71.6 vs 35.1 BAU/ml) (Figure 3). However, it was not statistically significant (p=0.09). There were also no statistically significant differences in the neutralising antibody reactivity post-first and second doses between convalescent and non-convalescent individuals (Table II). A post hoc power calculation was performed based on the observed effect size and sample size, which indicated that the study had 99.8% power to detect the observed differences at a significance level of 0.05.

After adjusting for confounders, there were still no significant differences in reactivity between convalescent and non-convalescent individuals. Nevertheless, we found age to be significantly associated with nAb reactivity at 3 weeks post-first dose (adjusted OR 0.96, 95% CI 0.92, 0.97, p<0.001). The differences were no longer significant after the second dose.

Median nAb titres reached its peak detectable limit for all vaccinated patients 1 month (mean 4.4 weeks) after the

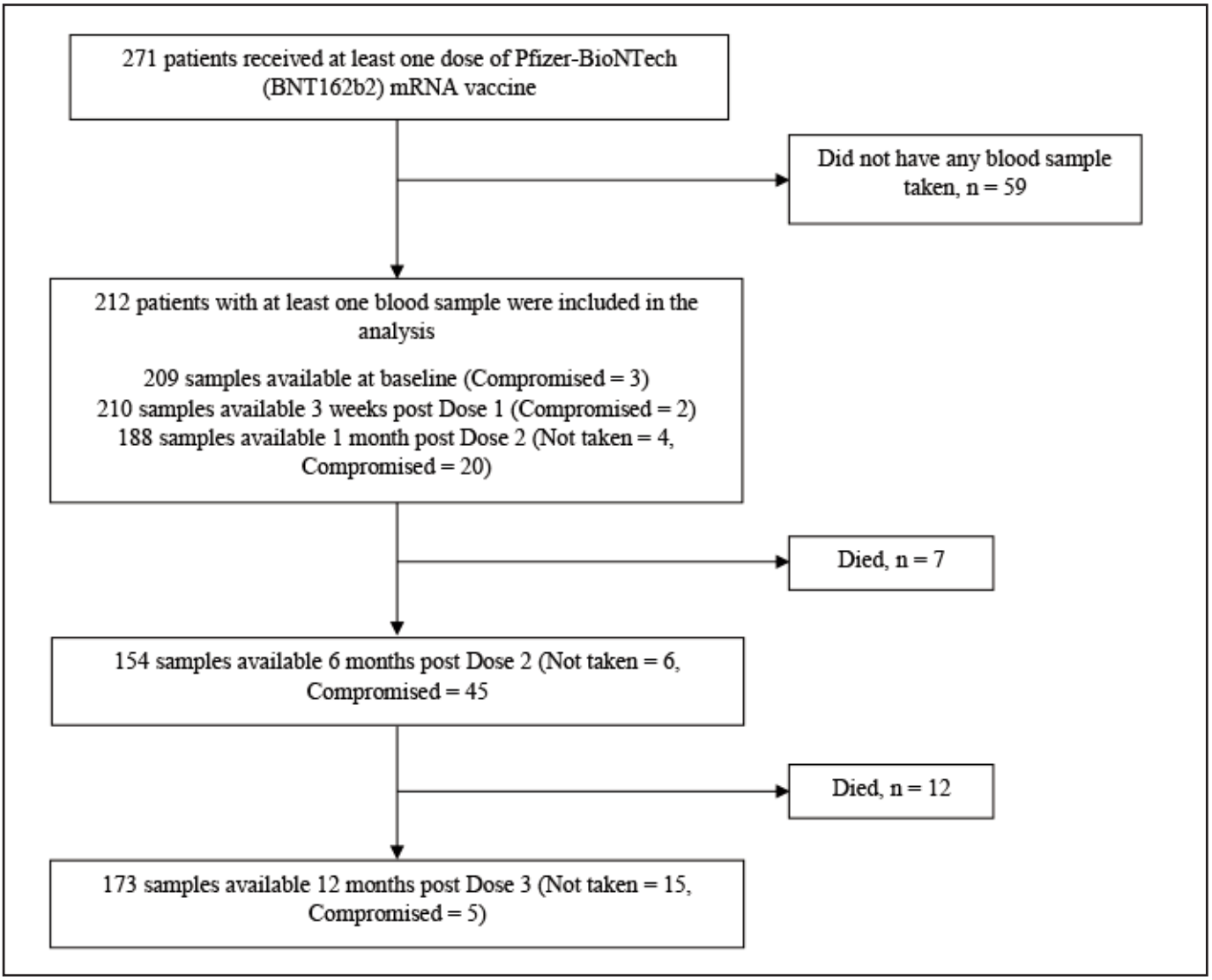

Fig. 2: Sample availability at each scheduled time point

second dose. The median level was reduced to 174.5 BAU/ml by the sixth month (mean 23.5 weeks). However, after the third dose, median nAb levels remained consistently high until the last observed sample 12 months later.

DISCUSSION

Patients with ESRD have compromised immune systems and comorbidities thus they are at a higher risk of severe COVID-19, and possibly reduced vaccine-induced antibody responses compared to the general population.[14,15]

We observed an almost complete seropositivity rate (98.4%) in our samples after two doses of the Pfizer- BNT162b2 vaccine compared to just one dose. Additionally, we found that patients with prior SARS-CoV-2 exposure had higher median nAb titres after the first dose of the vaccine, although this difference was not statistically significant. This finding is consistent with a study examining antibody responses after multiple doses of the same vaccine,[16] reinforcing the understanding that prior infection can prime the immune system, but vaccination provides a significant boost in antibody levels regardless of prior exposure. With two doses, the antibody titer levels in all patients reached the maximum detectable limit, further justifying the importance of completing the full vaccination course.

We also observed a waning in median nAb titres six months after the second dose, nevertheless levels were amplified and remained consistently high after the third (booster) dose. This supports the rationale behind booster dose recommendations, particularly for vulnerable populations, as emphasised by the "Coronavirus Disease 2019 (COVID-19)" (2023).[17] Our findings provide real-world evidence supporting this vaccination strategy in haemodialysis patients.

The occurrence of breakthrough infections is consistent with the understanding that while vaccination significantly reduces the risk, it does not completely eliminate the possibility of an infection. Breakthrough infection occurred in 29.3% of our patients, which was higher compared to other

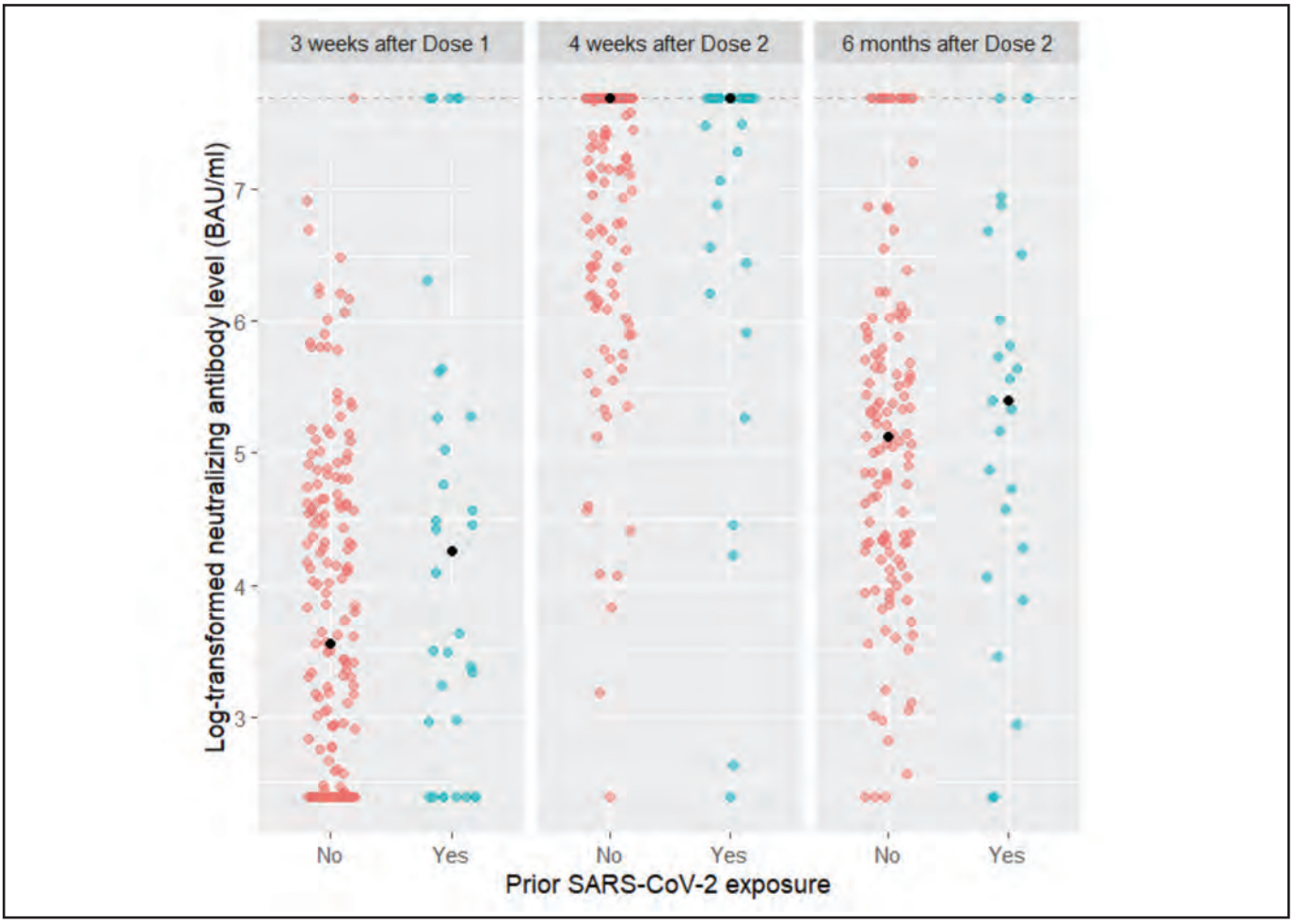

Fig. 3: Log-transformed neutralising antibody levels (BAU/ml) levels after doses 1 and 2 for those with and without prior exposure to SARS-CoV-2. The black circle indicates the median of the log-transformed antibody levels. The dotted grey line indicates the upper detection limit of the assay

studies in haemodialysis patients.[18,19] This discrepancy may be attributed to the study period and emergence of new variants that were either more contagious or more deadly. In mid to late 2021, the COVID-19 epidemic in Malaysia was dominated by the Delta variant before it was displaced by the highly transmissible Omicron variant in January 2022.[20] Most of the breakthrough infections in our cohort occurred after the third dose, coinciding with the period when the highly infective Omicron variant was widespread, which may explain the higher incidence rate observed.[21] Furthermore, this may reflect changes in individual behaviour and public practices following the relaxation of Malaysia's Movement Control Order (MCO). Nevertheless, there were no serious complications except in two cases where the patients died.

Limitations of the study

Our study has a few weaknesses. Firstly, breakthrough infection status was based on self-report. Infections were reported and documented, accompanied by test results, thus the likelihood of a false positive is reduced. If patients had symptoms during his clinic visit, his status would then be assessed by his treating nephrologist. Nonetheless, there may be particularly mild or asymptomatic cases that may have been missed. However, this limitation is unlikely to substantially affect the outcome of the study as the presence of asymptomatic infections itself may reflect an expected effect of vaccination which is known to attenuate disease severity even when infection is not fully prevented.

Secondly, blood-taking was done at fixed intervals rather than to the occurrence of breakthrough infections therefore we were unable to correlate levels of the antibody titres during the infection. Lastly, we did not conduct viral genotyping, therefore we were unable to determine which SARS-CoV-2 variants were responsible for the infections. Consequently, we could not assess whether immune responses differed depending on which variant patients were exposed to during the study.

CONCLUSION

Our results contribute to the growing body of evidence supporting the immunogenicity of this vaccine in haemodialysis patients. The high seropositivity rates and the sustained antibody levels after the booster dose underscore the importance of this vaccine in protecting this vulnerable population.

However, the occurrence of breakthrough infections highlights the need for continued monitoring, preventive measures, and further research to optimize vaccination strategies in haemodialysis patients.

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The artificial intelligence driven on the development of diabetic retinopathy prognostic scoring tool among type 2 diabetes mellitus patients: A review

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ABSTRACT

Introduction: Diabetic retinopathy, a major microvascular complication of type 2 diabetes mellitus, remains a leading cause of preventable blindness worldwide. Early identification of individuals at high risk is essential, yet conventional screening systems are limited by workforce shortages and delayed detection. Artificial intelligence, particularly machine learning, offers substantial potential to support prognostic scoring tools capable of predicting the development of diabetic retinopathy. This review summarises current evidence on AI-driven prognostic models for diabetic retinopathy among adults with type 2 diabetes mellitus.

Materials and Methods: A comprehensive PubMed search using Medical Subject Headings and free-text terms related to "Diabetic Retinopathy," "Type 2 Diabetes Mellitus," "Artificial Intelligence," "Machine Learning," and "Prognostic Model" was conducted. Original studies involving adults with T2DM that developed or evaluated AI- or ML-based prognostic or risk-scoring tools for DR were included. Extracted data included study design, sample size, artificial intelligence methods, predictors, and model performance, and were synthesised narratively.

Results: From 759 records, five studies met the inclusion criteria. Extreme Gradient Boosting consistently demonstrated the highest predictive performance, with area under the curve values between 0.803 and 0.966. Support Vector Machine also performed well in smaller cohorts. Key predictors across studies included HbA1c, duration of diabetes, renal function markers, blood pressure, lipid profile, and body mass index.

Conclusion: AI-driven prognostic tools show strong potential to enhance early diabetic retinopathy risk prediction. However, broader external validation and population-specific calibration are needed before routine clinical adoption.

KEYWORDS:
Type 2 Diabetes Mellitus, Diabetic Retinopathy, Prognostic Model, Artificial Intelligence, Risk Prediction

INTRODUCTION

Diabetic retinopathy (DR) is a significant and growing global health concern, recognized as a leading cause of vision loss among working-age populations. DR is a microvascular complication of diabetes mellitus, characterized by damage to the retinal blood vessels due to prolonged hyperglycaemia.[1] The global prevalence of DR among individuals with diabetes varies widely and is influenced by geographic location, socioeconomic status, and healthcare access. Recent studies estimate that approximately 34% to 40% of diabetic individuals worldwide are affected by DR, with this prevalence expected to rise alongside increasing rates of diabetes.[2] According to the National Diabetes Registry (NDR) of Malaysia, the proportion of patients diagnosed with DR increased from 10.6% in 2019 to 11.5% in 2020, illustrating a growing number of individuals at risk of visual impairment due to this complication.[3]

In Malaysia, DR screening is integrated into primary care, where all patients with diabetes undergo annual retinal assessment using non-mydriatic fundus cameras, which provide clearer images and higher diagnostic confidence compared to direct ophthalmoscopes.[4] Retinal images captured at Klinik Kesihatan are reviewed and will be graded as no DR, non-proliferative DR (mild to severe), proliferative DR, or diabetic macular oedema (DME). Patients with normal findings continue yearly screening, those with mild or moderate NPDR are referred non-urgently to ophthalmology, while severe NPDR, PDR, or suspected DME requires urgent referral.[5] However, constraints such as limited trained health personnel, equipment costs, and geographic accessibility challenges reduce DR screening efficiency.[6-8] Consequently, high-risk patients may remain unidentified until advanced stages of disease.

The use of artificial intelligence (AI), particularly machine learning (ML) models, for predicting and assessing the risk of DR among patients with type 2 diabetes mellitus (T2DM) has gained significant traction in recent years. ML models such as logistic regression, support vector machines, and deep learning techniques have shown promise in identifying risk factors associated with DR in T2DM patients. The performance of these models is often evaluated in terms of

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accuracy, sensitivity, and area under the curve (AUC) metrics. For example, several studies reported construction and assessment of models that achieve accuracy rates exceeding 80% when leveraging extensive datasets.[9] Furthermore, previous study done noted that certain ML algorithms offer superior prediction capabilities compared to traditional clinical methods due to their ability to uncover complex patterns within the data.[10]

In the context of Malaysia, leveraging AI-driven tools could address significant challenges faced in diabetic care. The Malaysian healthcare system, despite its advancements, still deals with barriers such as limited resources and disparities in healthcare access.[11] AI-driven tools can serve to mitigate these challenges by providing cost-effective screening solutions that are both accurate and scalable to the needs of the population.[12] The pressing need to address the high prevalence of DR among T2DM in Malaysia, and with the advancements in AI technology for disease management, makes this review both timely and critical. The aim of this review is to summarise existing evidence on AI-driven DR prognostic scoring models.

MATERIALS AND METHODS

A comprehensive search strategy was developed for the PubMed database using a combination of Medical Subject Headings (MeSH) and free-text terms. The key MeSH terms included "Diabetic Retinopathy," "Diabetes Mellitus, Type 2," "Artificial Intelligence," "Machine Learning," and "Deep Learning." These were combined with free-text keywords such as "prognostic model," "prediction tool," "risk score," "scoring system," "survival prediction," "algorithm," and "AI-driven model." Boolean operators (AND/OR) were used to refine retrieval, and truncation was applied where appropriate to capture variations of each term. The search strategy was designed to ensure optimal sensitivity and specificity for studies focusing on AI-driven prognostic or risk-scoring tools specifically targeting DR outcomes in T2DM populations. No date restrictions were initially imposed to allow broad coverage of emerging and foundational literature. However, only articles published in English and involving human subjects were included.

Study selection was guided by predefined eligibility criteria. Articles were included if they (i) involved adults diagnosed with T2DM, (ii) focused on DR as an outcome of interest, (iii) applied artificial intelligence, machine learning, or deep learning approaches to develop, validate, or evaluate prognostic or risk-scoring tools for DR, and (iv) were original research articles (e.g., cohort, cross-sectional, modelling studies, algorithm-development papers). Studies were excluded if they focused solely on image-based DR classification without prognostic intent, did not differentiate T2DM from other diabetes types, lacked AI-based methodological components, or were review articles, case reports, editorials, or conference abstracts.

All search results were screened by title and abstract, followed by full-text assessment of potentially relevant articles. Data extraction focused on study characteristics (authors, country, sample size, study design), AI methods used (algorithm types, predictors, model architecture), performance metrics, and relevance to DR prognostic. Extracted information was synthesized descriptively and thematically to capture methodological trends, model performance, clinical applicability, and gaps in the existing evidence base.

RESULTS

The search initially yielded 759 articles from the PubMed database. After applying the free full-text filter, 405 articles were available for further assessment. Title and abstract screening of these records narrowed the pool to 77 studies that appeared to align with the inclusion criteria of this review. Following a comprehensive full-text review, five studies were identified as specifically reporting on the development of AI-driven DR prognostic scoring tool. These five studies were subsequently included in the analysis for this review. Table I presents the summary of the key points extracted from the papers.

Across the five included studies, AI and ML models demonstrated strong potential in predicting DR among adults with T2DM. Sample sizes varied significantly from small clinical cohorts of fewer than 400 participants to very large datasets exceeding 32,000 hospital records. Despite this variation, all studies consistently showed that ML approaches outperform traditional statistical modelling when applied to complex, multi-variable clinical datasets. Overall, Extreme Gradient Boosting (XGBoost) emerged as the most consistently high-performing model. In the large-scale Chinese cohorts by Li et al. and Zhao et al., XGBoost achieved excellent discriminative performance, with AUCs of 0.90 and 0.803–0.966, respectively.[13,14] These models identified key predictors such as elevated HbA1c, nephropathy, serum creatinine, insulin treatment, and lipid abnormalities. Importantly, Zhao et al., demonstrated that the XGBoost model could predict incident DR nearly three years before clinical diagnosis, highlighting its value for early intervention and risk stratification.[14]

In medium-sized datasets, such as the Romanian cohort by Roșu et al., XGBoost also outperformed other models, achieving an AUC of 0.72 after hyperparameter tuning.[16] Cardiovascular risk factors, particularly systolic blood pressure, low-density lipoprotein (LDL) cholesterol, and body mass index (BMI) were repeatedly identified as important predictors. In contrast, the UK-based study by Kotsiliti et al., found that gradient boosting machines and random forest models performed best, with AUCs between 0.73 and 0.77, especially when longer-term HbA1c and ACR trends were incorporated, demonstrating the value of longitudinal biochemical data.[15]

The Taiwanese dataset analysed by Tsao et al., further supports the strength of AI models, showing that Support Vector Machines (SVM) achieved an AUC of 0.839, outperforming artificial neural networks and logistic regression.[17] This study highlighted clinically interpretable predictors such as insulin use and duration of diabetes, reinforcing their relevance across both traditional and machine-learning approaches.

Table I: Characteristics of The Included Studies

Authors	Year	Country	Study Design	Sample Size	Machine Learning Models Used	Performance Measures	Key Outcomes
Kotsiliti et al.,[15]	2017	United Kingdom	Population-based retrospective cohort using NHS Diabetic Eye Screening data	n = 6,375	Logistic Regression (LASSO), Random Forest, Gradient Boosting Machine, Regularised Gradient Boosting	AUC 0.73 ± 0.03 (10-fold CV). With 5-year HbA1c & ACR data: AUC 0.77 ± 0.04	A gradient boosting machine model using duration of diabetes, HbA1c, and age as predictors achieved a cross validated AUC of 0.73 in predicting diabetic retinopathy.
Roșu et al.,[16]	2024	Romania	Retrospective cross-sectional study	n = 377	Random Forest, XGBoost, Support Vector Machine, Logistic Regression	RF AUC = 0.62; XGBoost AUC = 0.68, improved to 0.72 after tuning	The XGBoost model was identified as the best prediction model with the highest AUC (area under the curve value, 0.90).
Tsao et al.,[17]	2018	Taiwan	Retrospective clinical dataset analysis	n = 536	Support Vector Machine, Decision Tree, Artificial Neural Network, Logistic Regression	Accuracy 79.5%, AUC = 0.839 (80/20 split). Slightly lower AUC with 60/20/20 split	The XGBoost model achieved the highest predictive performance for the risk of diabetic retinopathy among patients with type 2 diabetes with an AUC, accuracy, sensitivity, and specificity of 0.803, 88.9%, 74.0%, and 81.1%, respectively.
Li et al.,[13]	2021	China	Retrospective cohort study using electronic medical records	n = 32,452	Logistic Regression, Random Forest, Support Vector Machine, XGBoost (best)	XGBoost AUC = 0.90. Key predictors: HbA1c > 8%, nephropathy, creatinine >100 μmol/L	The XGBoost machine learning model showed the best predictive performance, with AUC of 0.72 after tuning, and SBP, HDL cholesterol, and BMI were consistently identified as the most important predictors across models.
Zhao et al.,[14]	2022	China	Retrospective cohort study with longitudinal follow-up	n = 7,943	XGBoost (best), Random Forest, Logistic Regression, Support Vector Machine, KNN	AUC = 0.803, Accuracy = 88.9%, Sensitivity = 74.0%, Specificity = 81.1%. Follow-up AUCs = 0.834–0.966	Support vector machines performed better than the other machine learning algorithms and achieved 79.5% and 0.839 in accuracy and AUC.

Notes: XGBoost = extreme gradient boosting, AUC = area under curve, CV = cross-validation, ACR = albumin-to-creatinine ratio, WBC = white blood cell, BMI = body mass index

Collectively, the studies demonstrate that machine-learning models, particularly XGBoost and SVMs provide reliable and often superior predictive accuracy compared with conventional methods. Common high-impact predictors across studies include HbA1c, duration of diabetes, renal function markers (creatinine, eGFR, ACR), blood pressure, lipid levels, BMI, and insulin therapy. These findings support the integration of AI-driven prognostic tools into DR screening pathways to enable more targeted follow-up, earlier detection, and personalised diabetes care.

DISCUSSION

Recent advancements in AI and ML have significantly improved the accuracy and performance of predictive models for DR among patients with T2DM. Various studies have explored diverse algorithms and methodologies, showing that AI can enhance early detection and improve patient outcomes through timely intervention. For instance, Yang et al., demonstrated the feasibility of ML classifiers based on non-ocular data for identifying referable DR in a large-scale rural population, highlighting the strong performance of algorithms like XGBoost and random forest in achieving high accuracy rates.[18] Similarly, Jiang and Li compared different ML algorithms, including XGBoost and SVM, and demonstrated their efficacy in predicting DR in T2DM patients, thus providing an alternative to traditional diagnostic methods.[19]

Glycaemic control is prominently recognized as a critical predictor of DR. HbA1c, a standard measure of long-term glycaemic control, has been consistently linked to the development and severity of DR. Patients with higher HbA1c levels tend to show more advanced stages of DR, highlighting its role in disease progression and risk assessment.[20] Additionally, studies reveal that poor blood glucose control aggravates microvascular complications, including DR, which progresses from non-proliferative to proliferative stages as glycaemic control deteriorates.[21] Renal function is another essential predictor, as diabetic nephropathy and DR often coexist, reflecting microvascular damage. Prolonged diabetes duration significantly correlates with increased risk of both diabetic nephropathy and DR, with modelling studies showing that a 5-year increase in diabetes duration raises the risk for chronic kidney disease (CKD) and subsequent DR.[22] Furthermore, the presence of albuminuria serves as a critical marker of renal impairment, indicating a compounded risk for DR.[23]

Blood pressure also plays a pivotal role in predicting DR development. Hypertension has been established as a risk factor for DR, with several studies demonstrating that elevated systolic and diastolic blood pressure levels contribute to the progression of diabetic microvascular complications.[24] The interaction between hypertension, metabolic syndrome, and diabetes complicates the clinical picture, as patients often present with concurrent dyslipidaemia, further impacting vascular health and exacerbating the risk for DR.[25] Lipids, particularly cholesterol and triglycerides, are also implicated in the pathogenesis of DR. Dyslipidaemic states characterised by elevated levels of LDL cholesterol and triglycerides, as opposed to high-density lipoprotein (HDL) cholesterol, have been associated with worsened retinal outcomes.[26]

ML approaches have made significant advancements in the prognostic modelling of DR, contributing to more accurate and timely diagnosis, thereby effectively mitigating the risks associated with this sight-threatening condition. The ML frameworks enable the integration of patient data to generate predictive models tailored to individual risk profiles. For example, recent studies have developed systems capable of predicting the progression of DR from fundus images with high accuracy.[27] Furthermore, the adaptability of ML models in handling diverse datasets makes them a practical choice for prognostic modelling. They can be trained on various datasets encompassing different populations and disease severities, which increases their generalizability across different clinical setups.[28] This adaptability is critical in fields like DR, where variability in patient demographics can significantly affect outcomes.

The clinical and public health implications of utilising AI-driven prognostic scoring models for DR are substantial, potentially enhancing early detection, treatment accuracy, and management efficiency. AI ML models have demonstrated optimal accuracy in diagnosing DR, often outperforming traditional methods. Certain AI ML models have achieved diagnostic sensitivities and specificities that rival those of expert clinicians, particularly in interpreting retinal images for signs of DR.[29] Additionally, AI-driven models are particularly advantageous in resource-limited settings, where expert human resources are scarce. Automation lowers the costs of DR grading, with studies indicating potential reductions in annual screening costs per patient.[30] Moreover, the integration of AI in DR screening significantly enhances patient outcomes and public health management. The use of AI technologies has been associated with improved patient compliance with screening protocols and increased accessibility of diagnostic services, particularly in rural and underserved regions.[31]

However, several limitations persist in the applicability of these models, primarily stemming from issues related to external validation, dataset diversity, algorithmic transparency, and clinical integration. One significant limitation of existing evidence lies in the inadequate external validation of AI-driven models. Many studies focus on internal validation using small datasets, which raises concerns regarding the generalizability of the findings to broader populations. For instance, a national real-world evidence study noted that while AI models exhibit promise in detecting DR, performance frequently declines when models are applied to external datasets, highlighting the variability in the effectiveness of these algorithms across diverse populations.[32] This limited external validity can lead to the overfitting of models, which might perform excellently on training datasets but poorly in actual clinical environments.[33]

Future research should prioritise prospective, multicentre validation studies to confirm the generalisability and real-world applicability of current AI-driven prognostic models across diverse healthcare settings and populations. There is also a need to integrate clinical predictors with retinal imaging, biochemical markers, and longitudinal electronic health record data, allowing models to capture both structural and physiological determinants of DR progression. In the Malaysian context, future work should focus on the development of locally calibrated prognostic scoring tools that reflect the unique demographic, ethnic, and clinical characteristics of T2DM populations in the country. Finally, adopting explainable AI approaches such as Shapley Additive Explanations (SHAP) values or interpretable ML frameworks will be essential to enhance clinician trust, facilitate clinical decision-making, and support successful implementation of AI models into routine screening and public health programmes.

CONCLUSION

This review demonstrates that AI-driven prognostic models hold substantial promise for improving early prediction of DR among adults with T2DM. ML algorithms, particularly XGBoost, consistently outperform traditional statistical approaches by integrating diverse clinical predictors such as glycated haemoglobin, renal function markers, blood pressure, lipid levels, and duration of diabetes. These models offer meaningful opportunities to strengthen risk stratification, optimise screening intervals, and support earlier intervention. However, most existing models are limited by inadequate external validation and a lack of population-specific calibration, underscoring the need for future multicentre, real-world studies to enhance generalisability and clinical applicability.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Challenges in delivering healthcare services among immigrants from Southeast Asia: A scoping review

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ABSTRACT

Introduction: Cross-border migration presents increasing challenges to healthcare systems globally. Ensuring equitable healthcare access for immigrant populations, particularly in Southeast Asia, requires a thorough understanding of the barriers to effective service delivery. This scoping review aimed to synthesize the existing literature on the challenges related to the delivery of healthcare services to immigrant communities from Southeast Asia.

While previous studies (e.g., Brandenberger et al., 2019) applied the 3C framework to migrants and refugees globally, this review generates new insights by focusing specifically on Southeast Asia, a region underrepresented in the literature. By applying the 3C model in this context, our review identifies region-specific challenges, such as immigration policies, financial barriers, and COVID-19 impacts, that extend beyond the findings of earlier global reviews.

Materials and Methods: A comprehensive search was conducted in ProQuest, PubMed, ScienceDirect, and Scopus databases on October 13, 2024, for studies published between January 1, 2011, and October 13, 2024. The search strategy used tailored keywords, including "challenges," "healthcare services," "immigrants," and "Asia." Inclusion criteria focused on peer-reviewed, English-language articles reporting on challenges in healthcare service delivery among immigrant populations in Southeast Asia. Data extraction and synthesis were guided by the 3C model: communication, continuation of care, and confidence in the healthcare system.

Results: The search identified 656 records, of which 7 studies met the inclusion criteria after a multi-stage screening process. Key challenges identified across the included studies were: Communication barriers, including language differences, cultural misunderstandings, and limited health literacy; Issues with continuation of care, such as poor health literacy, difficulties navigating healthcare systems, barriers to accessing services (e.g., due to legal status or financial constraints), and lack of coordination between healthcare and social services; and Lack of confidence in the healthcare system, stemming from distrust, lack of understanding, and negative experiences, including perceived discrimination.

Conclusion: This review highlights the complex challenges in delivering healthcare services to immigrants from Southeast Asia. These challenges, encompassing communication, continuation of care, and confidence, necessitate targeted and multifaceted interventions. Addressing these issues through culturally competent care, enhanced communication strategies, and policy reforms that promote equitable access is crucial for improving the health and well-being of immigrant populations and fostering more inclusive healthcare systems within the region.

KEYWORDS:
Healthcare access immigrants, Immigrant health challenges, Healthcare disparities, Southeast Asia immigrant health, Migrant health services

INTRODUCTION

Cross-border migration has garnered significant attention globally in recent decades. The International Organization for Migration (IOM) reports that the estimated number of international migrants reached 214 million, constituting approximately 3% of the global population.[1] By 2020, this number had increased, with Asia hosting 85.6 million migrants.[2] Achieving high-quality and equitable healthcare services requires extensive planning and effort to overcome the challenges and complications that come in the way of success. For many countries, this has been made more complicated by the surge of immigrants' influx.[3]

From the perspective of some local citizens, both undocumented and documented immigrants are viewed as a threat to the local population in terms of health, security, economy, and environment.[1] This perception can lead to the neglect of the rights of immigrants, particularly in receiving equitable healthcare services, and may result in discriminatory practices within healthcare settings. Effective healthcare service delivery necessitates clear communication. However, immigrants often face challenges such as language barriers, cultural differences, limited knowledge of the host country's healthcare system, financial constraints, and discriminatory practices. These challenges hinder effective communication, continuity of care, and trust in healthcare systems.[1,2]

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Specifically, previous research has identified language, cultural differences, and a lack of knowledge regarding the host country's healthcare system as common challenges faced by immigrants.[3] Further studies have highlighted issues such as financial constraints, referral problems, and police involvement,[4] as well as discrimination based on factors like religion, sex, and place of origin.[5] In Malaysia, studies have shown that access to healthcare services by immigrant communities is limited due to language barriers, financial issues, discrimination, and physical inaccessibility,[6] with similar challenges reported among non-citizen laborers.[7] A qualitative study in Malaysia also identified social and cultural differences, inadequate livelihood, health literacy, lack of knowledge about the healthcare system, and a lack of inclusivity for refugees and asylum-seekers as key barriers.[8]

To systematically explore these multifaceted challenges, this scoping review adopts the 3C framework, which encompasses Communication, Continuation of Care, and Confidence in the healthcare system. The 3C model, introduced by Brandenberger 2019, offers a comprehensive and patient-centered approach to understanding healthcare barriers among migrants and refugees.[27] It emphasizes the dynamic interplay between patient-provider interaction, system navigation, and institutional trust. This framework is especially relevant to immigrant populations, where language barriers, health literacy deficits, and cultural mismatches often converge to disrupt effective service delivery. Incorporating the 3C model allows for an organized synthesis of the literature, offering insights not only into the direct healthcare interactions but also into broader systemic and psychosocial factors affecting healthcare utilization.[11]

From the public health perspective, a shortfall in delivering healthcare services for vulnerable immigrant groups could have significant negative implications on the health of the local population. This is highlighted in the Sustainable Development Goals (SDG), which is to end some of the communicable disease epidemics by achieving Universal Health Coverage (UHC).[9] While previous studies applied the 3C framework to migrants and refugees globally, this review generates new insights by focusing specifically on Southeast Asia, a region underrepresented in the literature. By applying the 3C model in this context, our review identifies region-specific challenges, such as immigration policies, financial barriers, and COVID-19 impacts, that extend beyond the findings of earlier global reviews. This review aims to explore and synthesize existing literature on the challenges in delivering healthcare services to immigrant communities from Southeast Asia, using the 3C model (Communication, Continuation of Care, Confidence).

MATERIALS AND METHODS

This scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.[10] This framework ensures a transparent and systematic approach to mapping the existing literature on challenges in healthcare service delivery to immigrant populations.

Data sources and Searches

A comprehensive search was performed in ProQuest, PubMed, ScienceDirect, and Scopus databases on October 13, 2023, for studies published between January 1, 2011, and October 13, 2024 (i.e., from the end of 2010 to October 13, 2024), and limited to English language publications. The time frame (2011–2024) was used to include recent studies and reflect current healthcare challenges, including those during the COVID-19 pandemic. The search strategy was tailored to each database to maximize the retrieval of relevant articles. The following search terms were used as shown in Table I.

Eligibility Criteria

This review excluded studies with restricted or limited access. While this may have reduced the breadth of included literature, the decision ensured that all selected studies were accessible in full text for rigorous quality assessment and data extraction. This approach enhances transparency and replicability but may have introduced a limitation, which is acknowledged in the Discussion section.

The review included studies focusing on challenges in healthcare service delivery among immigrant populations from Southeast Asian countries. Studies were included if they were original, peer-reviewed articles published in English. The review excluded letters to the editor, conference papers, proceedings, and abstracts, as well as studies focusing on healthcare challenges outside the Southeast Asian region. Grey literature was excluded to ensure the review focused on peer-reviewed studies, which are generally more reliable, consistent, and scientifically validated. There were no eligibility limits for the population studied, the intervention used, the comparative parameters, the study results, or the study design. Only studies with open access or available through open archives were included, to ensure full-text availability for quality assessment and data extraction.

Study Selection

The second reviewer independently assessed 20% (n = 2) of the full-text articles for eligibility. The agreement rate between the primary and secondary reviewer was 100%, demonstrating strong consistency in the application of inclusion and exclusion criteria.

To ensure quality and consistency, 20% of the full-text articles were independently reviewed by a second reviewer. Inter-reviewer agreement was high, with minimal discrepancies that were resolved by consensus with a third reviewer.

Table I: Search Terms Used in This Scoping Review

(challenges OR barriers) AND (healthcare OR health services) AND (immigrants OR migrants) AND (Southeast Asia OR Asia Or Brunei OR Myanmar OR Cambodia OR Timor Leste OR Loas OR Malaysia OR Philippines OR Singapore OR Thailand OR Vietnam OR Indonesia)

Table V: Integrated Performance Measures for Output-Oriented BCC DEA Model

No	Title & Author's	Population	Country	Journal	Study Typology	Main objective	Main objective
1.	Preventive knowledge, attitude, and vaccination challenges for COVID-19 among Myanmar refugees and irregular migrants in Malaysia (Khai and Asaduzzaman, 2023) [12]	Myanmar irregular migrant workers and refugees 25 May to June 20, 2021	Malaysia	Vaccine: X	Mixed methods	To explore COVID-19 prevention knowledge, attitudes, and vaccination challenges among refugees and irregular migrants from Myanmar in Malaysia	Communication, Continuation of Care
2.	Perceived barriers of accessing healthcare among migrant workers in Thailand during the coronavirus disease 2019 (COVID-19) pandemic: a qualitative study (Uansri et al., 2023) [13]	Stakeholders from health and non-health sectors in Thailand from July to October 2021	Thailand	International Journal of Environmental Research and Public Health	Qualitative	To examine the key health concerns and barriers during the COVID-19 pandemic on healthcare access among migrant workers in Thailand through the lens of policymakers, healthcare professionals, experts on migrant health, and migrant workers.	Communication, Continuation of Care, Confidence
3.	Fever and health-seeking behaviour among migrants living along the Thai Myanmar border: a mixed-methods study (Khirikoekkong et al., 2023) [14]	Undocumented migrant workers, and cross-border villagers from Myanmar with high mobility and travel around the border area without official permits 14 June to 19 December 2019	Thailand/ Myanmar	BMC Infectious Diseases	Mixed methods	To investigate the concept of fever and the determinants influencing health–seeking behaviours among migrants on the Thai–Myanmar border, where rapid economic development collides with precarious political and socio–economic conditions	Communication, Continuation of Care
4.	Barriers to Health and Social Services for Unaccounted-For Female Migrant Workers and Their Undocumented Children with Precarious Status in Taiwan: An Exploratory Study of Stakeholder Perspectives Wang and Lin, 2023) [15]	12 stakeholders, well-versed in immigrants-related issues August 2019 and May 2021	Taiwan	International Journal of Environmental Research and Public Health	Qualitative	This study explores the accessibility and availability of social services for unaccounted-for female migrant workers and their undocumented children with precarious status	Continuation of Care
5.	Access to Health-Related Information, Health Services, and Welfare Services among South and Southeast Asian Immigrants in Japan: A Qualitative Study (Matsuoka et al., 2022) [16]	Foreign students September to November 2021	Japan	International Journal of Environmental Research and Public Health	Qualitative	To explore the barriers and promoting factors for their access to health-related information, health services, and welfare services during the first wave of COVID-19	Communication, Continuation of Care
6.	Factors influencing healthcare-seeking behaviour among Muslims from Southeast Asian countries (Indonesia and Malaysia) living in Japan: an exploratory qualitative study (Kohno et al., 2022) [17]	Muslims in Japan from Southeast Asian countries (Indonesia and Malaysia)	Japan	BMJ Open	Qualitative	To identify factors influencing healthcare-seeking behaviours and to explore issues with healthcare experiences of Muslims from Southeast Asian countries (Indonesia and Malaysia) living in Japan.	Communication, Continuation of Care, Confidence
7.	Health literacy as the missing link in the provision of immigrant health care: A qualitative study of Southeast Asian immigrant women in Taiwan (Tsai and Lee, 2016) [18]	Southeast Asian immigrant women and a wide range of stakeholders	Taiwan	International Journal of Nursing Studies	Qualitative	To explore and understand specific language and communication problems experiences by Southeast Asian immigrant women in Taiwan.	Communication, Continuation of Care, Confidence

Table III: JBI Critical Appraisal Checklist for Qualitative Research

No	Author	1	2	3	4	5	6	7	8	9	10	Score
1	Khai & Asaduzzaman (2023, Malaysia)	+	+	+	+	+	-	+	+	+	+	9
2	Uansri et al. (2023, Thailand)	+	+	+	+	+	-	-	+	+	+	8
3	Khirikoekkong et al. (2023, Thai-Myanmar border)	+	+	+	+	+	-	+	+	+	+	9
4	Wang & Lin (2023, Taiwan)	+	+	+	+	+	-	-	+	+	+	8
5	Matsuoka et al. (2022, Japan)	+	+	+	+	+	-	-	+	+	+	8
6	Kohno et al. (2022, Japan)	+	+	+	+	+	-	-	+	+	+	8
7	Tsai & Lee (2016, Taiwan)	+	+	+	+	+	-	+	+	+	+	9

Duplicates were removed from the electronic search results after they were exported to Microsoft Excel. The primary reviewer determined which studies should be included. One reviewer extracted data from full-text reviews, with another independently evaluating 20% of these papers to assess eligibility and consistency. Any disagreements about study inclusion were settled with the help of a third reviewer.

Data Extraction

Data from the included studies were extracted and summarized in a table format (Table II). Extracted data included information such as study country, context, sample, applied methodology, and study objectives. Figure 2 summarizes the review process using the PRISMA-SCR diagram.

Data Synthesis

The 3C model, as illustrated in Figure 1, comprising communication, continuation of care, and confidence in the healthcare system, served as the framework for synthesizing the findings of this scoping review.[11]

To clearly organize the results, we used the 3C framework, Communication, Continuation of Care, and Confidence, based on definitions from Brandenberger 2019.[27] We followed these simple rules:

- Communication: Included issues with language, health information, or cultural misunderstandings between patients and providers.
- Continuation of Care: Included problems with access to services, follow-up care, legal or financial barriers, and system navigation.
- Confidence: Included trust in healthcare, fear of discrimination, and whether patients felt respected or safe using services.

Each study's findings were reviewed and sorted into these categories based on what the challenges were mainly about. If a finding related to more than one area, we placed it in the most relevant category and discussed overlaps when needed.

RESULTS

Study Selection

The electronic database search yielded a total of 656 records. The distribution of records across the databases was as follows: 129 from ProQuest, 515 from ScienceDirect, 9 from PubMed, and 3 from Scopus. Following the removal of 424 records due to non-open access or irretrievability and 5 duplicates, 227 records remained. Title and abstract screening resulted in the exclusion of 216 records deemed irrelevant to the review topic. Eleven records underwent full-text review for eligibility assessment, and 4 records were subsequently excluded as they focused on challenges outside the Southeast Asian region. Consequently, 7 studies met all inclusion criteria and were included in this scoping review. The study selection process is illustrated in Figure 2.

Study Characteristics

The seven studies included in this review comprised five qualitative studies and two mixed-methods studies. The qualitative studies utilized methods such as in-depth interviews and focus group discussions. The studies focused on diverse immigrant populations, including migrant workers, refugees, and women in transnational marriages, originating from countries such as Myanmar, Thailand, Vietnam, and various Southeast Asian countries. The research settings varied, encompassing both urban and rural areas within countries like Malaysia, Thailand, Taiwan, and Japan. The publication years of the included studies ranged from 2014 to 2024. Key characteristics of the included studies are summarized in Table I.

Synthesis of Findings

The findings of this review, synthesized using the 3C model, revealed several challenges in the delivery of healthcare services to immigrant populations in Southeast Asia. These challenges are categorized under communication, continuation of care, and confidence in the healthcare system.

Communication

Challenges related to communication were consistently reported across the included studies.[12-14,16-18] These challenges manifested as language barriers between healthcare providers and immigrant patients.[13,18] Some studies highlighted difficulties in obtaining accurate medical histories and providing effective health education due to these language differences.[12,13,18]

Continuation of Care

Several factors impeded the continuation of care for immigrant populations.[12-18] These included limited health literacy among immigrants, which hindered their ability to navigate the healthcare system effectively.[17,18] Access to healthcare services was also affected by financial constraints[12,13] and, in some cases, by the lack of legal status.[14] Moreover, coordination between healthcare providers and social welfare was also reported as a further way to enhance attendance at medical appointments and reduce health information loss.[16]

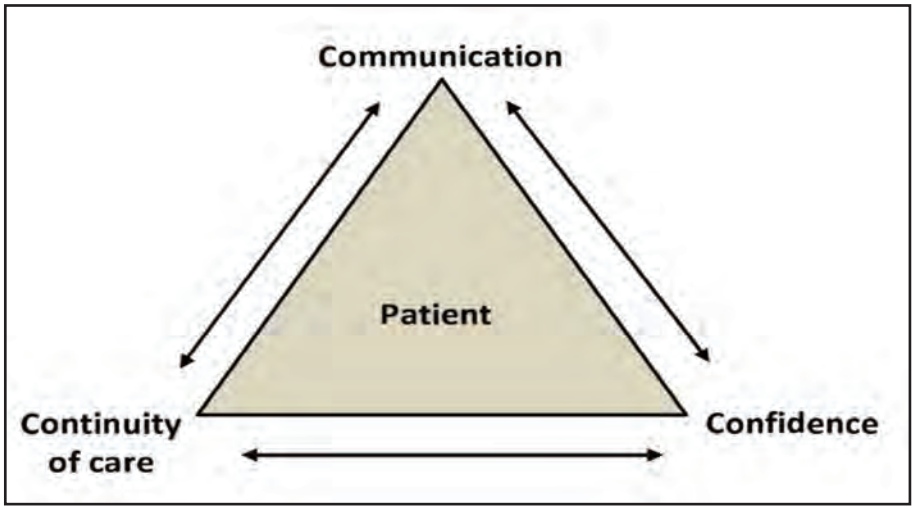

Fig. 1: Conceptual framework of the scoping review

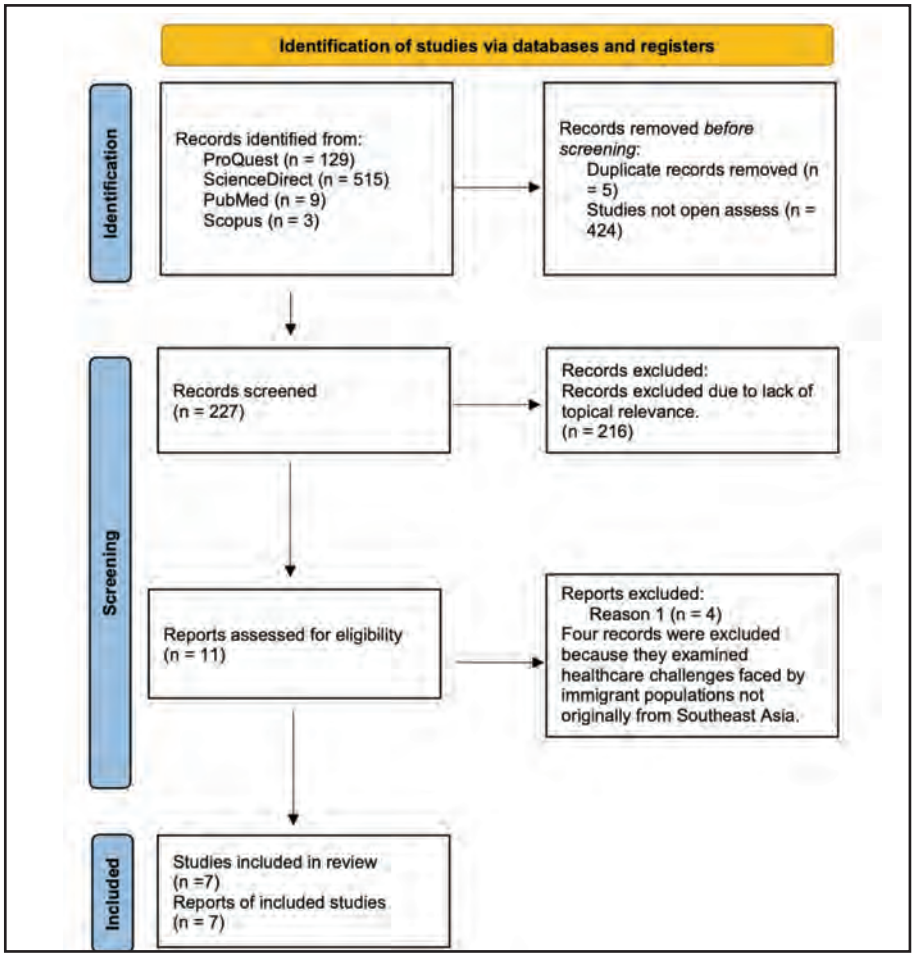

Fig. 2: PRISMA-SCR diagram of the reviewing articles

Confidence

Challenges related to confidence in the healthcare system were also identified.[13,17,18] These challenges included a lack of trust in healthcare providers and institutions.[17] Also, gaps in interpersonal communication skill and significant service adjustment as happened during the COVID-19 pandemic can further drive them away from accessing proper healthcare.[13,18] In addition, negative experiences with healthcare services, including perceived discrimination, contributed to this lack of confidence.[13]

DISCUSSION

This scoping review sought to determine the challenges related to the delivery of healthcare services for immigrant communities in Southeast Asia. The review's findings,

synthesized through the 3C model (communication, continuation of care, and confidence in the healthcare system), illuminate the complex and interconnected nature of these challenges.

Communication

Communication, a cornerstone of effective healthcare delivery, presents multifaceted challenges for immigrant populations. Our review consistently identified language barriers, cultural misunderstandings, and limited health literacy as significant impediments to accessing and utilizing healthcare services.

Language barriers are a pervasive issue, creating difficulties in the interaction between healthcare providers and immigrant patients. This finding is consistent with a previous systematic review which also highlighted language as a key challenge.[3] Similarly, studies in other regions have also underscored language as a major obstacle, reinforcing the global relevance of this issue.[19,20] The inability to communicate effectively hinders accurate history taking, diagnosis, and the provision of appropriate health education and counselling. Also, previous studies illustrated that these linguistic challenges could compromise the quality of care and lead to misunderstandings that erode trust and impede treatment adherence.[13,18]

However, the communication challenges extend beyond mere linguistic proficiency. Cultural differences profoundly influence health beliefs, practices, and help-seeking behaviours. Studies highlighted that even when immigrants possess some level of host-country language skills, navigating the healthcare system can be challenging due to a lack of understanding of the specific cultural norms and expectations within healthcare settings.[16,17] This aligns with Concilio, Costa who also stated that migrants' access to healthcare services in foreign countries is challenging due to insufficient language proficiency, cultural understanding and systemic awareness. Healthcare systems are often designed around the dominant culture, and immigrants may encounter difficulties in understanding healthcare information, expressing their concerns, and participating in decision-making processes. This can lead to feelings of alienation, disempowerment, and a reluctance to engage with healthcare services.[21]

Furthermore, limited health literacy exacerbates communication challenges. Many immigrants may have low levels of health literacy, which hinders their ability to obtain, process, and understand basic health information and services. This can result in difficulties in navigating the healthcare system, understanding treatment plans, and engaging in preventive care. As highlighted in our review, low health literacy interacts with language and cultural barriers to create a complex web of challenges that impede effective communication and access to care.[15,18]

Our review also brought to light the additional vulnerability faced by undocumented migrants, who often experience significant communication barriers due to fear of legal repercussions and limited access to regulated health services.[12] This vulnerability may lead them to seek alternative, unregulated sources of care, such as self-medication or traditional healers, which can pose risks to their health.[14]

It is also important to acknowledge the role of healthcare providers in facilitating effective communication. As reported by Uansri, Kunpeuk [13], negative attitudes and lack of cultural competence among healthcare staff can create communication barriers and erode trust among immigrant populations. Professionalism and empathy are crucial in engaging with clients regardless of background status.

In addressing these multifaceted communication challenges, healthcare systems must implement comprehensive strategies that include providing access to professional language interpretation services, promoting cultural competence training for healthcare providers, and developing culturally appropriate health education materials. Community-based interventions that utilize cultural brokers or community health workers can also be effective in bridging the communication gap and improving access to care for immigrant populations.[22]

Continuation of Care

Ensuring the continuation of care for immigrants presents a complex set of challenges, intricately linked to health literacy, access to healthcare services, and effective institutional collaboration. Our review underscores the interplay of these factors in shaping the experiences of immigrant populations within Southeast Asia.

Health literacy plays a pivotal role in enabling individuals to navigate healthcare systems effectively and engage in appropriate self-care practices. As highlighted by Brandenberger, Tylleskär (11), health literacy, or the education of migrants and refugees about the host country's healthcare system, is critical for enabling these individuals to traverse varied healthcare landscapes effectively. However, language barriers, cultural differences, and a lack of familiarity with the host country's healthcare system can significantly impede health literacy among immigrants. This is consistent with findings in Malaysia, where health literacy and lack of knowledge about the healthcare system were identified as key barriers.[8] As demonstrated by another studies, language barriers not only hinder communication between providers and patients but also limit immigrants' ability to access and understand health information, leading to difficulties in managing their health and utilizing healthcare services appropriately.[17,18] For example, migrant clients in Japan may have the hassle of being turned down by the emergency department if they are visiting the facility without using an ambulance.[17]

Access to healthcare services is a fundamental determinant of health and well-being, and our review highlights the significant barriers that immigrants face in accessing care. Financial constraints, including poverty, unemployment, and lack of health insurance, are major impediments to accessing healthcare services.[6,13] These financial barriers are often exacerbated by unstable employment and limited access to social support, particularly during crises such as the COVID-19 pandemic.[23] Furthermore, the absence of legal

status creates additional barriers to accessing care, as undocumented immigrants may fear detention, deportation, or denial of services.[12,14] The fear of accessing healthcare due to legal repercussions is a significant concern, particularly when referring a patient to a high facility level, such as a hospital.[14]

Effective coordination and collaboration between healthcare providers and social welfare agencies are crucial for ensuring continuity of care and addressing the complex needs of immigrant populations. As Matsuoka, Kharel (16) suggested, this coordination is crucial for ensuring migrants have access to necessary healthcare services and that their health information is maintained and transferred appropriately between various points of care. Immigrants often require a range of social services, including housing, employment, and legal assistance, in addition to healthcare services. Integrated care models that facilitate communication and collaboration between different sectors can improve access to services, enhance care coordination, and address the social determinants of health. This is particularly important for vulnerable subgroups within the migrant population, such as women and children, who may face additional challenges related to prenatal care, vaccinations, and legal status.[15]

Addressing these challenges requires a multi-faceted approach that includes strengthening health literacy among immigrant populations, reducing financial and legal barriers to healthcare access, and promoting integrated care models that facilitate collaboration between healthcare and social services. Policy interventions aimed at expanding health insurance coverage, providing language assistance services, and supporting community-based health programs can improve access to care and promote health equity for immigrant populations.

This study advances the application of the 3C framework by situating it within the Southeast Asian context, highlighting unique barriers not emphasized in previous reviews. These include the intersection of undocumented status with healthcare denial, culturally specific health-seeking behaviors among migrant subgroups, and the compounding effect of the COVID-19 pandemic. Thus, our review contributes new knowledge by contextualizing the 3C model to a region facing distinct migration patterns and healthcare governance structures.

Confidence

Confidence in the healthcare system is crucial for immigrants to engage with and utilize healthcare services effectively. Our review highlights the factors that influence confidence, including trust in healthcare providers and institutions, a sense of agency within the healthcare encounter, and the impact of healthcare system design and delivery.

Trust in healthcare providers and institutions is a cornerstone of the patient-provider relationship and a key determinant of healthcare utilization and adherence. As highlighted by Simpson (24), this trust is developed through a combination of personal encounters and an overall belief in the system's ability to respond to one's specific requirements. However, immigrants may experience a lack of trust due to various factors, including communication barriers, cultural misunderstandings, and negative experiences within the healthcare system. Language barriers and low health literacy can contribute to misunderstandings and a perception of being treated unfairly, eroding trust and creating a sense of alienation.[25] As indicated by Kohno, Dahlui (17), gaps in interpersonal communication can further drive them away from accessing proper healthcare. Negative experiences, such as perceived discrimination or lack of cultural sensitivity among healthcare providers, can also undermine trust and create a reluctance to seek care. As reported during the peak of the pandemic, negative attitudes among staff towards migrants, represents a breakdown in professionalism and empathy.[13]

A sense of agency, or the ability to control a situation, is also essential for fostering confidence in the healthcare system. Migrants often experience a loss of control due to language barriers, lack of understanding of the healthcare system, and power imbalances in the patient-provider relationship.26 When healthcare systems are not designed with the needs of a diverse population in mind, especially during crises like the pandemic, this loss of control and autonomy becomes even more pronounced, driving migrants further away from accessing care.[13] This can lead to feelings of disempowerment and a reluctance to engage with healthcare services.

The design and delivery of healthcare services also play a crucial role in shaping immigrants' confidence in the system. Healthcare systems that are not responsive to the needs of diverse populations, that lack cultural competence, or that are perceived as discriminatory can erode trust and create barriers to care. Significant service adjustment during the COVID-19 pandemic attributed partly to the constraints in the health system design of the host country in catering to migrants led them to be turned away when seeking healthcare.[13]

Building confidence in the healthcare system requires a multi-faceted approach that addresses the factors that undermine trust and agency among immigrant populations. This includes promoting cultural competence among healthcare providers, ensuring access to language assistance services, and creating healthcare environments that are welcoming, inclusive, and responsive to the needs of diverse populations. Community engagement and participatory approaches can also be effective in building trust and empowering immigrant communities to engage with healthcare services.

Strength

This scoping review has several important strengths. By applying the 3C framework (Communication, Continuation of Care, and Confidence) in the Southeast Asian context, it highlights barriers not emphasized in previous reviews, such as healthcare denial among undocumented migrants, culturally specific health-seeking behaviors, and the impact of the COVID-19 pandemic. This adds new knowledge beyond earlier global studies.

The review also follows PRISMA-ScR guidelines, ensuring a transparent and rigorous process. Its regional focus on

Southeast Asia fills a key gap, as most existing reviews emphasize high-income countries. By focusing on countries like Malaysia, Thailand, Japan, and Taiwan, the findings provide contextually relevant insights for policymakers and practitioners.

Lastly, by identifying gaps such as the limited data on undocumented migrants and the need for more non-COVID studies, this review sets a clear foundation for future research and policy development to improve immigrant health outcomes.

STUDY LIMITATION

A key limitation was the exclusion of restricted-access studies, which may have contained relevant insights. Including both open and restricted-access studies in future reviews could provide a more complete understanding of the challenges.
This review also has other limitations. The included studies varied in methods, populations, and healthcare settings, which reduces the generalizability of the findings. Focusing only on English-language publications may have excluded relevant studies in other languages, suggesting that future reviews should include multilingual sources. In addition, most of the studies were conducted during the COVID-19 pandemic, which may have influenced the findings. Future research should address these issues by using more diverse populations, multilingual approaches, and exploring challenges beyond the pandemic context.

CONCLUSION

This scoping review elucidates the complex challenges in delivering healthcare services to Southeast Asian immigrant communities. Guided by the 3C model, the findings reveal persistent barriers in communication, continuity of care, and trust in healthcare systems, issues compounded by language barriers, cultural differences, limited health literacy, and systemic inequities. To address these multifaceted challenges, policymakers and healthcare practitioners must prioritize the development and implementation of culturally tailored interventions. This includes investing in professional medical interpreters and multilingual health materials to overcome language barriers, training healthcare providers in cultural competence to build trust, and establishing care coordination programs to ensure seamless continuity of care. Furthermore, policy reforms should focus on reducing systemic inequities by enhancing access to affordable healthcare services and integrating community health workers who bridge cultural gaps. By adopting these targeted strategies, healthcare systems can improve outcomes for immigrant populations, promote equity, and foster a more inclusive and responsive regional healthcare infrastructure.

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Closing the gaps in obesity: The need for a strategic, system-wide approach to obesity care in Malaysia

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ABSTRACT

Introduction: The global obesity epidemic threatens health systems worldwide and is associated with severe health complications such as cardiovascular disease, type 2 diabetes, and cancers, imposing substantial economic burdens. Globally, over 1.9 billion adults are classified as overweight, with 650 million identified as obese.

Materials and Methods: A review was conducted using academic databases and authoritative reports from organizations such as the WHO and the Institute for Public Health. Studies published between 2002 and 2024 were selected based on methodological rigor and relevance to obesity in Malaysia.

Results: Malaysia has the highest obesity rate in Southeast Asia and has classified obesity as a chronic disease. Currently, 21.8% of Malaysian adults are affected by obesity – a fivefold increase from 4.4% in 1996 – with projections reaching 41% by 2040. Obesity-related healthcare costs consume 10-20% of Malaysia's national budget. Malaysia joined the Obesity Policy Engagement Network (OPEN) and implemented a model-of-care survey to gather healthcare professional insights and identify critical obesity management gaps. This initiative aimed to provide evidence-based recommendations to enhance patient outcomes and alleviate economic strain on the healthcare system. The Malaysian OPEN survey indicated that only one-third view obesity as a disease, resulting in underinvestment in necessary infrastructure and treatment options such as pharmacotherapy and bariatric surgery. These prevailing misconceptions among healthcare professionals and decision-makers hinder progress. A collaborative, multidisciplinary strategy supported by robust policies and evidence-based research is thus vital in managing obesity as a chronic disease.

Conclusion: Addressing obesity in Malaysia requires a collaborative, multidisciplinary approach that integrates lifestyle, behavioural, medical, and surgical strategies. Policy reform, stakeholder engagement, and evidence-based planning are essential to improve patient outcomes, reduce economic burdens, and ensure equitable access to care. A unified national effort is vital for sustainable and effective obesity management.

KEYWORDS:
Behavioural therapy; Early medical interventions; Malaysia; Obesity; Stakeholder participation

INTRODUCTION

Obesity is a chronic and multifactorial disease with significant health implications, driven by dietary changes, physical inactivity, socioeconomic factors, and genetic predispositions. The global obesity epidemic is a pressing public health challenge, with obesity rates soaring over the past few decades. The World Health Organization (WHO) estimates that worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled. In 2022, 2.5 billion adults were overweight, and 890 million were living with obesity.[1,2] In Malaysia, the percentage of overweight individuals consistently increased from 29.4% in 2011 to 32.6% in 2023, with intermediate rates of 30.0% in 2015 and 30.4% in 2019 while the obesity rate rose from 15.1% in 2011 to 21.8% in 2023, reaching 17.7% in 2015 and 19.7% in 2019.[3] According to Malaysia's National Health and Morbidity Survey (NHMS) 2023 report, the prevalence of overweight and obesity among Malaysian adults is influenced by various social determinants of health.[4,5] According to this report, overweightness was commonly observed in individuals from urban areas (34.6%), those aged ≥60 years (40.7%), men (36.7%), and those with an income above RM10,000 (36.0%).[4,5] In contrast, obesity was more prevalent among urban residents (36.4%), middle-aged population (46.3%), women (39.8%), and individuals earning between RM8,000 and RM9,999 (38.6%).[4,5] Obesity was also reported to be more prevalent in specific demographic groups, such as Chinese retirees and Indian homemakers.[3]

Addressing obesity with the same urgency as other non-communicable diseases (NCDs) is critical in Malaysia, given its role in over 200 chronic diseases, including 54.8% (231 million) of cardiovascular diseases (CVD)[6], 30% (1 million) of type 2 diabetes (T2D)[7], 28.2% of metabolic dysfunction-

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associated fatty liver disease (MAFLD)[8,9] and various cancers.109 Effective obesity management could yield substantial savings, with estimates starting at RM25 billion in 2024 and reaching RM736 billion by 2035.[10,11] In 2017, total expenses of RM8 billion accounted for 10.7% of GDP, and accounting for only 7.4% of total spending in Malaysia. By 2035, the projected costs are expected to reach RM100 billion, which is equivalent to 7.4% of GDP, covering 96.2% of total expenditures. Additionally, obesity-related losses in 2035 are estimated to result in RM3.2 trillion in disability-adjusted costs.[12,13]

To address this nationwide issue of obesity, Malaysia participated in the Obesity Policy Engagement Network (OPEN) and Awareness, Care & Treatment in Obesity Management (ACTION) survey. The OPEN survey, conducted globally, included countries such as Canada, Brazil, Germany, Turkey, Australia, Spain, and Italy, allowing for a comprehensive evaluation of obesity care approaches across various healthcare systems. Malaysia survey was designed to identify the gaps in Malaysia's current obesity management strategies by engaging key stakeholders, including HCPs (endocrinologists, general practitioners, primary care physicians, cardiologists, and practice nurses who had >10% of their patient population consisting of patients with obesity, PwO) and healthcare decision-makers (HCDMs), including commissioners, heads of departments, hospitals, clinics, or practices, and member of national or regional health committee. as well as PwO.[14] On the other hand, the ACTION Malaysia survey included HCPs from internal medicine, general practice physicians, cardiologists, endocrinologists/diabetologists, gastroenterologists, as well as nutrition specialists, family physicians, obstetricians/gynaecologists and aesthetic specialists.[15] The results of both these surveys identified critical barriers in treatment approaches in Malaysia and emphasized the need for collaborative frameworks to enhance obesity management within Malaysia's healthcare system.[14,15] Key findings highlighted the importance of improving communication between healthcare providers and people with obesity, addressing mental health considerations, and developing culturally tailored strategies.[14,15]

Based on findings from the OPEN and ACTION surveys, this review article has been developed to elucidate critical issues in obesity management, such as reclassifying obesity as a disease, tackling obesity stigma, promoting healthy lifestyles, and recognizing the efficacy of pharmacotherapy and surgery. By comparing national practices with global standards, this review article aims to provide essential evidence-based insights to inform policy development, ultimately aiming to improve patient outcomes and mitigate the economic and healthcare burdens associated with obesity.

MATERIALS AND METHODS

A review was conducted in continuation with a white paper on obesity management in Malaysia to synthesize current knowledge about obesity in Malaysia.[16] Multiple electronic databases, including PubMed, Scopus, and Google Scholar. The search was deliberately broad to capture the nuanced landscape of obesity research while maintaining a focus on the Malaysian context.

RESULTS AND DISCUSSION

Current challenges for effective obesity management

1. Misconceptions and stigma

Both the OPEN survey and the ACTION survey results highlighted that most HCPs (54%) and HCDMs (51%) in Malaysia had significant bias and misconceptions about obesity. About 55% of HCPs and 57% of HCDMs believed that obesity is solely the result of personal behavior.[14,15] According to the ACTION study, only 44% of the HCPs discussed their obesity concerns with patients who had very high BMI cut-off values, while 43% alerted their patients based on visual assessment, and about 49% of HCPs identified obesity as a possible risk factor when patients had comorbidities.[8,14] These implicit biases harboured by HCPs may cause them to dismay or downplay the concerns of their patients, especially the obese patients. This in turn, can lead to less aggressive treatment plans and reluctance to refer patients to specialists, ultimately compromising the quality of care.

The ACTION survey results further highlighted that stigmatization within the healthcare system can further exacerbate the problem, as obese patients may feel judged or shamed, discouraging them from seeking care or adhering to treatment recommendations.[14] Cultural perceptions, such as "No Nasi Lemak, No Life!" reflect entrenched attitudes toward food that can perpetuate unhealthy eating habits in patients and diminish the perceived urgency of addressing obesity as a serious health issue. As long as obesity remains stigmatized, it will continue to be perceived with limited awareness as a risk factor for metabolic diseases.

2. Resource allocation

Often, obesity is not prioritized as a critical public health issue, leading to insufficient funding for prevention and treatment programs. This issue was highlighted in the OPEN survey results, wherein it was shown that HCDMs had selective areas for funding allocations, which may not always align with the needs of comprehensive obesity management.[15] The study further showed that HCDMs perceived current allocations of funds towards obesity as somewhat skewed towards preventions rather than treatment (Figure 1).[15] About 40% of HCDMs preferred allocating their budgets for secondary prevention 38% to self-management 38%, and only 34% to primary prevention. Only 32% of HCDMs allocated funds for screening and diagnosis, and long-term management, while only 26% allocated funds to treating obesity.[15] Underfunding of public health initiatives exacerbates these issues, as campaigns and community-level interventions lack focus, lustre and are therefore not impactful. The absence of robust policies in Malaysia further restricts access to multidisciplinary care, specialized treatments, and necessary medications or surgeries, thus complicating the efforts toward obesity management.[15] These gaps in current policies have inadequately tackled the environmental and societal factors contributing to obesity, such as non-adherence to the food pyramid and inadequate physical activity infrastructure, which further impedes efforts to combat obesity.

3. Training and awareness about obesity amongst HCPs
As per the OPEN survey results, only 59% of the HCPs and 53% of the HCDMs opined that obesity care in Malaysia is well-organised and that these patients deserve equal care.[15] The results also demonstrated that 54% of the HCPs believed that they received limited education on obesity during their medical training; this leads to an incomplete understanding of the complex nature of the disease, including the biological, psychological, and social aspects. Only 46% of the HCPs reported having received over 20 hours of obesity-related training during the post-graduate and undergraduate education.[15] Thus, there is a shortage of trained professionals, resulting in inadequate treatment and poor patient outcomes in Malaysia.

4. Patient engagement
When obesity is not adequately addressed within the healthcare system, it leads to delays in effective treatment, allowing related complications like T2D and CVD to worsen. This often results in poor patient engagement, as patients may feel unsupported and demotivated, which negatively impacts their treatment adherence and health outcomes. According to the OPEN survey results, only 43% of patients in Malaysia feel comfortable discussing obesity with their HCPs.[15] This highlights the need for a more patient-centred approach to foster open communication about obesity management. Many patients lack accurate information and proper guidance on weight management, particularly beyond dietary modifications and lifestyle changes, and rely on social media and other online sources.[14]

5. Poor intersectoral coordination
Ensuring intersectoral coordination in obesity management presents several challenges, particularly in achieving coherence across ministries and aligning various stakeholders. Perceptions of both HCPs and HCDMs often influence their decisions toward treatment, resource allocation, and policymaking. In the OPEN survey study, only one-third of HCPs and HCDMs viewed obesity as a disease, while the majority perceived it as a result of personal choice rather than a complex condition with genetic, environmental, and psychological factors (Figure 2).[15] As a result, there is no prioritization of the necessary investments in treatment, education, training, or infrastructure needed for effective obesity management. Addressing these misconceptions is crucial for a more effective and empathetic approach to managing obesity.

Health reform pillars and strategies
The success of obesity management relies not only on individual efforts but also on addressing broader systemic challenges involving all parties, including HCPs, HCDMs, and patients. Effective obesity management involves a balanced combination of lifestyle changes, medical interventions, and behavioural therapies that could lead to sustained weight loss and better health outcomes in patients. Health reform pillars and strategies for obesity management ensure that patients have access to necessary resources, conducive environments, and support systems that foster healthy living and optimal obesity management. Equally important is establishing a robust monitoring and evaluation framework to track progress, assess outcomes, and inform continuous improvement in obesity care. Key health reform strategies include advancing health promotion and disease prevention, ensuring equitable healthcare access, transforming healthcare service delivery, and strengthening the foundation of the health system.[1]

Advancing health promotion and disease prevention
This approach focuses on shifting the healthcare paradigm from preventing obesity and reactively treating its complications to proactive intervention and prevention of obesity and its complications. This would reduce the incidence of obesity and its related complications, thereby lowering long-term healthcare costs and improving the overall health of the population.

Public awareness and training
Public education campaigns are vital in raising awareness about the causes and consequences of obesity. These campaigns should focus on educating the public about the health risks associated with obesity, including CVD, T2D, cancers, and other comorbidities. In addition, it is also important to emphasise that being overweight and obesity are preventable, that prevention is better than cure, and that obesity-related complications are reversible with proper interventions. Utilizing various media platforms, including social media, can help reach diverse demographic groups with tailored messages that resonate with their specific needs and concerns.

Promoting healthy lifestyles
The cornerstone of obesity management is the promotion of healthy lifestyles. Public health campaigns should target the population with clear, evidence-based information on the importance of balanced healthy nutrition and reduction of sedentary behaviour with regular physical activity. These campaigns could include guidelines on portion control, the benefits of consuming whole foods over processed foods, and the risks associated with excessive intake of sugar and high-calorie, low-nutrient foods. Community-based programs (local fitness initiatives, healthy cooking workshops, and active living events) encourage people to adopt healthier habits that help prevent overweight and obesity.

Addressing social determinants
Social determinants (income, education, and access to healthy food options) play a significant role in the risk of obesity. Addressing these determinants is critical in promoting health equity and preventing obesity. Policies that improve access to affordable healthy foods, create safe spaces for physical activity, and provide education and employment opportunities can help reduce the disparities that contribute to higher obesity rates in certain communities in Malaysia.

Evaluating and monitoring outcomes
To ensure the effectiveness of health promotion and disease prevention strategies, it is essential to implement robust evaluation and monitoring frameworks. These frameworks should track key indicators such as obesity prevalence, physical activity levels, and dietary habits across different population groups. Regular assessments should be done to identify the effects of these initiatives and refine strategies that may need adjustment. Continuous improvement in

Table I: Most common (voted by >40% of HCPs) support measures for obesity management recommended by HCPs in Malaysia

Support Measure	% of HCPs recommending it
Appropriate infrastructure/ equipment	59
Measures that allow patient feedback into services and provision of care for obesity	59
Maternal health programs for women living with obesity who are pregnant or considering pregnancy	59
Information/training to raise awareness of weight bias and stigma and tackle misconceptions that may be preventing care	58
Pharmacy-based care enabling patients with obesity to obtain information about their obesity treatment, support with managing their disease and/ or monitoring of signs and symptoms	58
Access to clinical practice guidelines on obesity for HCPs	57
Patient educational material/resources	57
Home healthcare services available to patients with obesity who are disabled by their disease	56
Access to professional networks for those HCPs involved with obesity care	55
Access to community-based healthcare that can deliver care and support patients with obesity closer to their home	55
Access to diagnostic tests for obesity risk assessment	55
Comprehensive screening of patients	55
Sufficient clinical and social referral pathways for patients with obesity	55
Relevant educational resources for clinical staff to deliver effective care	53
Comprehensive, well-defined diagnostic criteria	53
Framework that gives those supporting patients enough capacity (time) to care for patients with obesity	51
Digital health records enabling access to patient health data	50
Wearable technology for tracking patients' progress and monitoring their health	48
Incentive structure for HCPs, which allows prioritization, treatments, and long-term management of PwO	47
Personalized digital health tool /mobile app that enables patients with obesity to self-manage	46
Telehealth consultation	43

Table II: Most common (>15% of HCDMs) recommended topics to be included in obesity-related clinical practice guidelines

Topic of Interest	% of HCDM recommending it
Diagnosis and risk assessment	28
Psychological counselling	28
Nutrition	26
Disease progression	26
Physical activity	25
Long-term management of obesity	25
Early diagnosis	21
Surgical interventions	19
Pharmacotherapy	17

Table III: Top five measures incentivized (funded) by the Malaysian government or health authorities towards obesity management

Measure	% of HCDMs recommending it
Change in school food and nutrition policies	40
Awareness campaigns for educating the common man on obesity	39
Legislation policies for front-of-package labelling of food packets	38
Health promotion campaigns	37
Food and nutrition policies for the public	36

health promotion efforts are necessary to contribute to sustained progress in reducing obesity rates and improving public health outcomes.

Equitable healthcare access

Perceptions of obesity service accessibility differ; in the OPEN survey, 69% of HCPs believed that healthcare services are widely available, in contrast to 49% of HCDMs agreeing to it.[15] The NHMS 2023 report highlighted that while nearly three-fourths of medical care is available in public hospitals, 54.4% of patients have to bear out-of-pocket (OOP) expenses, and only 15% are covered by insurance in Malaysia.[8] The OOP model limits obesity treatment access, especially in rural areas, exacerbating healthcare disparities.

Increasing investments in health

Obesity care costs stem from treatment, prescription drugs, and chronic disease management. A 5% reduction in obesity prevalence could reduce the global economic costs by 5.2% annually (2020–2060).[17] Malaysia's 2024 health budget allocated RM 41.2 billion, with RM 465 million for outsourcing, ICT maintenance, and health screenings and mental health services. 18 However, healthcare spending (4.38% of Malaysia's GDP) remains lower than regional peers, while OOP costs (32.08%) are among the highest. Investments in obesity care should focus on upgrading facilities, digital infrastructure, medical training, and public awareness to alleviate the growing burden.[17]

Improving hospital care services

The current Malaysian clinical practice guidelines (CPG) in obesity present a comprehensive overview of obesity management, yet these are unable to provide practical aspects of an effective multidisciplinary framework.[14] Key issues, such as ineffective referrals, poor patient communication workflow, and disruptions in continuity of care after hospital discharge, contribute to delays in follow-up treatments and unnecessary readmissions. Most HCPs have indicated that some support measures are available to aid in delivering effective treatment and managing long-term care, but more needs to be done to streamline the process. (Table I).[15] Malaysia can draw some valuable lessons from Singapore's weight management programs, which incorporate personal consultations, diet management, exercise therapy, and behavioural modifications in a multidisciplinary setting. To enhance obesity treatment in Malaysia, it is crucial to improve access to pharmacotherapy and bariatric surgery within a well-coordinated, multidisciplinary care model. Setting clear goals for interventions is essential in evaluating the success of obesity treatment initiatives.

Currently, most clinicians and surgeons in Malaysia work in isolation. Implementing nationwide electronic medical record (EMR) systems can enhance connectivity between HCPs, improve access to specialists, reduce unnecessary referrals, and support more accurate diagnoses, effective treatments, and ongoing health education.[19] The EMR platform can provide several benefits, including evidence-based logistics management for treatment purchase and distribution, reducing strain on the healthcare system by minimizing unnecessary rehospitalizations and repeated diagnoses. Additionally, it provides comprehensive patient data to support the effective functioning of multidisciplinary teams.

Making comprehensive services affordable

A major challenge in providing comprehensive obesity services is the shortage of trained HCPs and resources. In the OPEN survey study, 50% of HCPs and HCDMs in Malaysia have acknowledged the need for improved support and resources. Approximately 57% of HCPs and 49% of HCDMs had cited limited primary care; 50% of HCPs and 49% of HCDMs pointed to a shortage of specialists as a challenge in managing obesity effectively.[15]

Effective obesity education needs to be broad-based, involving primary care providers, specialists, and allied health professionals.[1,20,21] Malaysia is committed to ensuring healthcare access for all citizens, focusing on low-income and rural populations. However, time and human resource constraints remain significant barriers to care. The key barrier in obesity treatment reported by 56% of HCPs and 45% of HCDMs is having sufficient capacity (time) for patients.[15] To address these gaps, there is a pressing need to expand and enhance obesity facilities and resources. This includes establishing more dedicated obesity clinics and support centres across various regions, particularly in underserved areas. Enhancing these facilities would involve investing in advanced diagnostic tools, treatment technologies, and specialized training for HCPs. There is an unmet need for more multidisciplinary teams, including dietitians, psychologists, and exercise physicians and physiologists, would also to improve the quality of care of these patients with obesity.

Additionally, developing telemedicine platforms can help bridge the gap between patients and HCPs, especially in remote areas where access to specialized care is limited. Improving obesity management infrastructure and resource allocation is essential for creating a more equitable and effective healthcare system. This approach not only addresses the immediate needs of patients but also builds a sustainable framework for long-term obesity management and prevention. Financial barriers significantly impede access to obesity treatment. Expanding insurance coverage to include anti-obesity medications (AOMs) can encourage more patients to seek treatment. For instance, insurance can extend to cover AOMs like GLP-1 agonists (semaglutide or liraglutide) to prevent the risk of CVD or T2D in obese patients. Insurance policies should consider BMI thresholds and the suitability of treatments for patients with various comorbidities.[22]

Enhancing healthcare spending efficiency

Improving the cost-effectiveness of obesity management involves personalizing pharmacotherapy and addressing the financial barriers to treatment compliance. Research shows that the duration of AOMs is usually shorter during the weight loss initiation phase than in the maintenance phase.[23] After achieving sustained weight loss, more affordable alternatives, such as weight-maintenance programs, behavioural health programs, or nutritional support, should be considered. Educating patients on the importance of treatment and the value offered by pharmacotherapy can help them navigate the cost barriers and switch treatments once weight loss is stabilized.24, 25 Additionally, shifting from high-cost AOM to lower-cost, long-term weight-maintenance programs can make treatments more accessible, especially for disadvantaged populations. Implementing value-based reimbursement models, where manufacturers and distributors are reimbursed based on treatment outcomes and efficiency, could also drive the supply of high-quality, cost-effective treatments.[25]

Transforming healthcare service delivery

National and international CPGs play a crucial role in shaping obesity care plans. In the OPEN survey study, both HCPs as well as HCDMs in Malaysia acknowledged the availability of dedicated CPG for obesity management.[15] However, earlier studies have shown that there is a notable gap in their perceived adequacy and usage in Malaysia.[26] According to the OPEN survey, only about 23% of HCPs and 53% of HCDMs use the CGP in obesity services.[15] Most HCDMs also indicated that the current CPG guidelines on obesity management do not provide much clarity on some key elements of holistic obesity care (Table II).[15]

Prioritizing primary health care

Addressing obesity effectively requires a strong emphasis on primary healthcare. General practitioners should serve as gatekeepers, integrating primary and specialized care and fostering strong relationships with specialists through hands-on teaching. Formal continuing medical education (CME) programs, trainee integration, and informal knowledge

transfer opportunities should be prioritized to ensure all HCPs are well-equipped to manage obesity. This paper underscores the pivotal role of primary care as the first point of contact for patients within the community. Primary care providers are essential in ensuring equitable access to healthcare services, facilitating early identification and management of obesity, and coordinating timely referrals for comprehensive, multidisciplinary care at secondary and tertiary levels of the health system.

Improving inter-sectoral coordination

Effective inter-sectoral coordination necessitates stakeholder engagement, policy prioritization, multi-sector collaboration, and partnerships with national authorities, non-government organizations (NGOs), academia, and the private sector. Key strategies include knowledge transfer among physicians through case discussions, joint consultations, and CME. MYOS is an association dedicated to HCPs involved in obesity care and management in Malaysia. It plays a critical role in garnering professional and public support for policy endorsement and implementation.

Effective obesity management requires collaboration across multiple sectors, including healthcare, education, transportation, and urban planning. For instance, schools can integrate comprehensive nutrition education into their curricula and ensure that meals provided are balanced and nutritious. Urban planners can design walkable neighbourhoods with accessible parks and recreational facilities, encouraging physical activity among residents. By fostering partnerships among these sectors, we can create environments that support healthy behaviours and reduce the incidence of obesity.

Leveraging digital technologies

Digital health technologies are revolutionizing obesity management with tools such as mobile apps, wearable devices, and online platforms. These innovations offer personalized guidance on diet, physical activity, and weight management and enable remote monitoring by HCPs for ongoing support and plan adjustments. Integrating these technologies into public health strategies can enhance obesity management by providing real-time feedback and motivation.[27]

The key benefits of digital tools are enhanced communication, effective monitoring, and comprehensive data sharing. For instance, the "Ramadan, T2D and Me" mobile app exemplifies how health technology can deliver health advice and glucose monitoring and highlights its effectiveness in public health interventions. This app assists diabetics during the fasting period by providing a blood sugar tracker and offers tips for diabetes management throughout the holy month of Ramadan.[27]

Strategies for tracking progress and evaluating outcomes

The primary focus of monitoring health reform in Malaysia is to reduce the prevalence of obesity in the country. A comprehensive approach to obesity management focuses on advancing obesity prevention strategies alongside implementing clinical reforms in obesity care. The goal is to align Malaysia's obesity rates more closely with other Southeast Asian countries, such as Singapore (11.6%) and Vietnam (18.3%).[28] Beyond reducing obesity rates, the broader objectives include alleviating the health and financial burdens of obesity and reducing obesity-related comorbidities. However, managing obesity presents two main challenges: patient and disease-related factors reflecting the complexity and diverse needs of obese patients, and contextual factors such as healthcare system constraints that impact collaboration among HCPs.

A collaborative care model involving an interdisciplinary team of endocrinologists, bariatric surgeons, general practitioners, clinical psychologists, researchers, nurses, and physiotherapists is essential. Each team member brings specific expertise to manage both the clinical and psychological aspects of obesity. Effective collaboration requires identifying individual roles and defining shared responsibilities, which involves co-managing patient care, consulting regularly to share information, developing patient care plans, and reviewing cases together. This integrated approach ensures well-rounded, holistic, patient-centred care.

Strengthening policies, legislation, and regulations

Policies should incentivize fitness and establish a multidisciplinary approach to obesity management, supported by legislation and regulations. Healthcare resources could be directed towards multidisciplinary teams that emphasize low-calorie diets, intensive behavioural therapy, and improved access to pharmacotherapy. Successful examples include Singapore's Healthy Meals in Schools Program and National Step Challenge, as well as Malaysia's nutrition labelling mandates and sugar-sweetened beverage taxes. According to the OPEN survey results, the top five measures that government or health authorities have set out or incentivized (funded) to prevent and manage obesity are elucidated in Table III.[15]

Promoting research and evidence-based approaches

Promoting research and evidence-based approaches is critical. Currently, 80% of obesity research is conducted in local universities, but only 22% of this research is relevant to developing new modalities and evaluating the effectiveness of interventions.[29] Research priorities should expand beyond the epidemiology of obesity, focusing on sociocultural factors, under-represented groups such as minority ethnicities and the elderly, and involving stakeholders like GPs, policymakers, and researchers. Cost-effectiveness studies should be planned to maximize coverage and benefits at the lowest possible cost, such as optimizing AOM interventions and streamlining the approval processes to expedite clinical trial applications and ensure timely publication of results. The ultimate goal of research should be to enhance avenues for multidisciplinary teams, develop new intervention studies, improve diagnosis, and incorporate new technologies, all while continuously refining policies to improve outcomes.

CONCLUSIONS

Malaysia faces significant health and financial challenges due to high obesity rates, with projections indicating that

healthcare costs could reach RM108 billion by 2024. Immediate and strategic action is essential to prevent the healthcare system from being overwhelmed. Effective policy implementation requires coherence across ministries, stakeholder alignment, and a clear framework for monitoring and evaluation. This involves setting clear goals, timelines, and ownership for projects, supported by incentives and long-term capacity building. Accountability is enforced through defined roles and outcomes, with interdisciplinary teams and stakeholder networks facilitating collaboration. Continuous feedback through site visits, calls, reports, and surveys is crucial for refining strategies and improving policy effectiveness. The strategic plan for obesity management is divided into three phases: short-term (2024-2026) focusing on clinical approaches, medium-term (2027-2029) on prevention and accessibility, and long-term (2030-2034) on sustaining and expanding efforts. These comprehensive reform strategies converge to advance health promotion, equitable financing, and service delivery. By promoting evidence-based clinical interventions, including pharmacotherapy and surgery, we aim to improve health outcomes. Simultaneously, it strengthens the healthcare system through interdisciplinary collaboration and clear accountability. If executed effectively, these strategies promise significant impacts, reducing healthcare costs and enhancing citizens' quality of life. Malaysia's commitment to this strategic path holds the key to a healthier, financially resilient future.

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CONFLICT OF INTEREST

None

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

The role of apolipoproteins as genetic biomarkers in schizophrenia: A systematic review

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ABSTRACT

Introduction: Schizophrenia is a complex mental disorder involving genetic, environmental, and neurodevelopmental factors. Despite significant progress in identifying several genetic contributors to schizophrenia, the role of apolipoprotein in lipid metabolism, neurodevelopment, and neuroprotection remains underexplored. This systematic review aims to synthesise existing genetic studies on apolipoproteins associated with schizophrenia to clarify their potential role in the disorder's pathogenesis.

Materials and Methods: A comprehensive literature review was conducted using the PubMed and Scopus databases, involving studies published from 2004 to 2023, and limited to English. Keywords included "schizophrenia," "apolipoprotein," "genetic," and "genetics." Non-research publications such as books, reviews, editorials, letters to editors, short communications, book series, chapters, and conference proceedings were excluded from this review. Only peer-reviewed journal articles were selected to ensure the reliability and credibility of the systematic review.

Results: A total of 41 articles were included in the review, with four key themes identified. The themes addressed specific aspects of apolipoproteins in schizophrenia, including their role in schizophrenia susceptibility, lipid metabolism, and cognitive functions within the disorder. This review presents a novel synthesis of these studies, focusing on the underexplored roles of apolipoprotein genes, including *APOE*, *APOL*, *APOD*, *APOA*, *APOC*, *APOER2*, and *APOBEC*, in schizophrenia.

Conclusion: This systematic review provides a comprehensive understanding of the genetics of apolipoprotein in schizophrenia, particularly in relation to lipid metabolism. The findings suggest future research directions to enhance the understanding of schizophrenia pathogenesis and highlight the importance of targeted research to identify specific genetic biomarkers for therapeutic interventions.

KEYWORDS:
Genetics, apolipoprotein, lipid metabolism, schizophrenia, systematic review

INTRODUCTION

Schizophrenia is a complex, multifactorial neuropsychiatric disorder influenced by genetics, environment, and neurodevelopment.[1] According to the World Health Organisation, in 2022, this condition affects approximately one in 300 people worldwide, or around 24 million individuals.[2] Those with schizophrenia experience symptoms such as hallucinations, delusions, disorganized thinking, and cognitive impairment.[3] While the heritability of schizophrenia is estimated to be as high as 80%, the specific genetic pathways contributing to its development remain only partially elucidated.

A growing body of research links lipid dysregulation to cognitive dysfunction and structural brain abnormalities in schizophrenia. Apolipoproteins are key regulators of lipid transport, cholesterol homeostasis, neuroinflammation,[4] neuronal repair, and synaptic plasticity.[5] Given these roles, apolipoprotein genes are biologically plausible candidates in schizophrenia, as variations in these genes may affect neurodevelopmental pathways, inflammatory responses, and metabolic profiles, all of which are implicated in the disorder.

Apolipoproteins comprise several families, including *APOA, APOBEC, APOC, APOD, APOE, APOER2*, and *APOL*. Although apolipoprotein E *(APOE)*, particularly ε2, ε3, and ε4 alleles, has been investigated extensively in neurodegenerative disorders,[6] the other apolipoprotein genes have recently attracted attention for their potential involvement in schizophrenia. However, their collective roles in disease susceptibility, cognitive outcomes, treatment response, and metabolic disturbances remain inadequately explored.

A previous systematic review focused mainly on the genetics of *APOE* in schizophrenia.[7] To date, no systematic review has

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synthesised the broader family of apolipoprotein genes or evaluated their potential as genetic markers in schizophrenia. Since apolipoproteins affect pathways linked to both psychiatric pathology and metabolic side effects of antipsychotics, a comprehensive synthesis is necessary to clarify their biological and clinical relevance. This systematic review aims to fill that gap by assessing existing research on apolipoprotein families in schizophrenia, offering a clearer understanding of their potential roles as genetic indicators. Specifically, this review aims to answer the following questions:

1. Which apolipoprotein genetic variants may serve as potential biomarkers of schizophrenia susceptibility and diagnosis?
2. Which variants may influence clinical course or predict treatment response?
3. Which variants may predict metabolic abnormalities commonly observed in schizophrenia, particularly those associated with antipsychotic therapy?
4. Which variants may predict cognitive performance or impairment among individuals with schizophrenia?

By synthesizing findings across multiple apolipoprotein gene families, this review seeks to provide a clearer understanding of their potential roles as genetic biomarkers in schizophrenia.

MATERIALS AND METHODS

Review Protocol

This systematic review involves formulating the research questions using the PICo method: 'P' for Problem or Population, 'I' for Interest, and 'Co' for Context, which is a tool employed by authors to develop research questions for the review.[8,9] A systematic document search was conducted in three phases: identification, screening, and eligibility.[10] The review also includes data extraction and qualitative data analysis.[9] Throughout the process, the authors consider alternatives to ensure alignment with the aim of the review.

Formulation of Research Question

Based on the PICo concept, the authors incorporated three major elements into the review population (P) of schizophrenia patients, interest (I) in genetic studies, and the context (Co) of apolipoprotein. This framework directs the formulation of the main research question: What are the genetic studies related to apolipoprotein in schizophrenia?

Identification

Two investigators (WNFWMZ and NEHAR) conducted a systematic search strategy using PubMed and SCOPUS databases. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The search strategy was developed using relevant keyword recognition, including "genetic," "schizophrenia," and "apolipoprotein," as detailed in the search string in Table I. All possible synonyms were included using appropriate Boolean operators and filters. The search was conducted on January 9th, 2025.

Screening

Original articles from peer-reviewed journals published in English between 2004 and 2023 were included. Non-research documents such as reviews, editorials, letters to the editor, short communications, books, book series, chapters, and conference proceedings were excluded to avoid potential bias and ensure that only studies with rigorous methodologies were considered. Two reviewers (NAT and MAK) independently screened all records retrieved during the search using predefined inclusion and exclusion criteria. Duplicate records and studies that did not satisfy the requirements were all discarded. Inter-rater reliability for the full-text screening stage was assessed using Cohen's kappa statistic. Out of 66 screened articles, the reviewers agreed on 58 decisions (87.9% observed agreement), yielding a Cohen's κ value of 0.642, indicating substantial agreement.[11] All eight disagreements were resolved through consensus.

Eligibility

A comprehensive evaluation of full-text articles was conducted to confirm their relevance to the study. Articles were excluded based on criteria such as irrelevance to the research topic, unclear methodologies, or deviations from the scope of the study. This process was followed by a detailed data appraisal to establish the eligibility of the remaining articles (Figure 1).

Risk of Bias and Quality Assessment

The articles were evaluated by two independent experts (NAT and MAK), focusing on the study design, methodology, sample size representativeness, and data analysis. The methodological quality of the observational studies was independently assessed by two reviewers (NEHAR and WNFWMZ) using the Newcastle–Ottawa Scale (NOS), which evaluates three domains: Selection, Comparability, and Exposure, with a maximum score of nine stars. Any scoring discrepancies were resolved through consensus with a third reviewer. Overall, the studies ranged from fair to good quality based on the NOS. Most studies demonstrated appropriate selection of cases and controls, although several lacked clear adjustments for confounding factors. The final NOS ratings are presented in Table II. Disagreements in extracted data were resolved through discussion, with a third reviewer arbitrating if necessary. Inter-rater reliability was also evaluated for the data elements. The non-human mechanistic studies (e.g., mouse and Drosophila models) were not assessed using NOS, as this tool is designed explicitly for human observational studies. These studies were instead narratively evaluated.

RESULTS

Background of Selected Studies

The study examined a total of 41 research articles which evaluated fifteen apolipoprotein-related genes. The frequency analysis revealed that the majority of the articles focused on *APOE* (n=25), making it the most heavily studied. This was followed by apolipoprotein L, *APOL* (n=6), apolipoprotein A, *APOA* (n=4), and apolipoprotein D, *APOD* (n=4). In contrast, other apolipoprotein genes, such as apolipoprotein C, *APOC* (n=2), apolipoprotein E receptor 2, *APOER2* (n=2), and apolipoprotein B editing enzyme catalytic, *APOBEC* (n=1), were investigated less frequently. Some studies investigated multiple genes reflecting varying research interests.

Thematic analysis was performed to provide a clearer

Table I: Search strings used in the selected database

Databases	Keywords used
Scopus	(TITLE-ABS-KEY ("genetic" OR "genetical" OR "genetically" OR "genetics" OR "genetics" OR "genetics") AND TITLE-ABS-KEY ("schizophre-nia" OR "schizophrenia" OR "schizophreni-as" OR "schizophrenia s") AND TITLE-ABS-KEY ("apolipopro-teine" OR "apolipoproteins" OR "apolipopro-teins" OR "apolipoprotein")) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
PubMed	("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms] OR ("genetic"[All Fields] OR "genetical"[All Fields] OR "genetically"[All Fields] OR "genetics"[MeSH Subheading] OR "genetics"[All Fields] OR "genetics"[MeSH Terms])) AND ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields]) AND ("apolipoproteine"[All Fields] OR "apolipoproteins"[MeSH Terms] OR "apolipoproteins"[All Fields] OR "apolipoprotein"[All Fields])

Table II: Quality Assessment of All Included Studies Using Newcastle-Ottawa Scale

No	Study	Selection (0-4)	Comparability (0-2)	Exposure (0-3)	Total (0-9)	Quality
1	Moberg et al. (2006)[13]	4	2	2	8	High
2	Kampman et al. (2004)[14]	4	1	2	7	High
3	Kecmanovic et al. (2010)[15]	4	1	2	7	High
4	Martorell et al. (2008)[16]	3	1	2	6	Moderate
5	Akanji et al. (2009)[17]	3	1	2	6	Moderate
6	Tovilla-Zarate et al. (2009)[18]	2	1	2	5	Moderate
7	Al-Asmary et al. (2015)[19]	3	1	2	6	Moderate
8	Vila-Rodriguez et al. (2011)[20]	0	0	2	2	Low*
9	Knickmeyer et al. (2014)[21]	0	0	2	2	Low*
10	Ormel et al. (2020)[22]	0	0	2	2	Low*
11	Zhang et al. (2006)[23]	4	1	2	7	High
12	Takahashi et al. (2008)[24]	4	1	2	7	High
13	Carrera et al. (2010)[25]	4	1	2	7	High
14	McGhee et al. (2005)[26]	3	1	2	6	Moderate
15	Dong et al. (2012)[27]	3	1	2	6	Moderate
16	Lee et al. (2013)[28]	3	1	2	6	Moderate
17	Hwang et al. (2013)[29]	3	1	2	6	Moderate
18	Shishido et al. (2023)[30]	3	1	2	6	Moderate
19	Suzuki et al. (2008)[31]	0	0	2	2	Low*
20	Tomita et al. (2007)[32]	0	0	2	2	Low*
21	Smith et al. (2008)[33]	3	2	2	7	High
22	Hong et al. (2012)[34]	3	2	2	7	High
23	Ban et al. (2017)[35]	3	2	2	7	High
24	Clark et al. (2009)[36]	3	1	2	6	Moderate
25	Vik-Mo et al. (2009)[37]	3	1	2	6	Moderate
26	Kao et al. (2014)[38]	2	2	2	6	Moderate
27	Li et al. (2020)[39]	2	2	2	6	Moderate
28	Fan et al. (2021)[40]	3	1	2	6	Moderate
29	Li et al. (2021)[41]	2	2	2	6	Moderate
30	Li et al. (2021)[42]	2	2	2	6	Moderate
31	Verbrugghe et al. (2012)[43]	4	2	2	8	High
32	Vila-Rodriguez et al. (2017)[44]	4	2	2	8	High
33	Hansen et al. (2006)[45]	3	2	2	7	High
34	Ward et al. (2017)[46]	3	2	2	7	High
35	Walker et al. (2006)[47]	3	1	2	6	Moderate
36	Boer et al. (2010)[48]	3	1	2	6	Moderate
37	Kurian et al. (2011)[49]	3	1	2	6	Moderate
38	Jonas et al. (2019)[50]	2	2	2	6	Moderate
39	Rao et al. (2021)[51]	3	1	2	6	Moderate
40	Liebers et al. (2016)[52]	2	2	2	6	Moderate
41	Rapp et al. (2010)[53]	0	0	2	2	Low*

Note: Quality categories: High (7-9), Moderate (5-6), Low (0-4).
* Different study design (not traditional case-control)

understanding of the main points of the articles.[54] The four main themes synthesised from the selected studies include: (1) Apolipoprotein E variants and schizophrenia susceptibility, (2) Apolipoprotein-related genetic interaction in schizophrenia, (3) Apolipoprotein variations' influence on lipid metabolism in schizophrenia, and (4) Apolipoprotein variants and cognitive function in schizophrenia. The results of each theme are discussed in the following sections.

Table III: Classification of articles according to Theme 1

Author (Year)	Author (Year)	Sample Size (n)	Methods	Genetic analysis	Genes	Key findings	p-value
Ormel et al.[22] (2020)	In vitro study (induced microglia-like cells)	20 Scz 20 Ctrl	RNAseq	GE	*APOE*	No association observed in iMG model derived from schizophrenia patients.	$p > 0.05$
Al-Asmary et al.[19] (2015)	Case-control	180 Scz 200 Ctrl	PCR	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε2 allele increase, while the ε3 allele decrease in schizophrenia patients.	$p \leq 0.01$
Knickmeyer et al.[21] (2014)	Cross-sectional (neonate's brain imaging)	248 neonates with parental psychiatric history	MALDI-TOF MS	SNP. genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3ε4 heterozygotes show reductions in brain volumes.	$p < 0.01$
Vila-Rodriguez et al.[20] (2011)	Case-control (postmortem brain study)	35 Scz 35 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	Similar allele and genotype frequencies as general population.	$p > 0.05$
Kecmanović et al.[15] (2010)	Case-control	76 Scz 82 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	No association in allele and genotype frequencies in schizophrenia.	$p > 0.05$
Akanji et al.[17] (2009)	Case-control	207 Scz 165 Ctrl	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3ε2 genotype and allele ε2 are less frequent in patients compared to controls.	$p = 0.04$
Tovilla-Zarate et al.[18] (2009)	Family-based association study	60 families (sibling pairs)	PCR-RFLP	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε3 allele is associated with schizophrenia patients, especially in females, whereas haplotypes of *APOE* ε3/*APOE*-219 G/T are associated with reduced schizophrenia risk in males. The *APOE*-ε2 allele is protective against early-onset schizophrenia.	$p < 0.05$
Martorell et al.[16] (2008)	Case-control (SNP association study)	585 Scz 615 Ctrl	MALDI-TOF MS	SNP genotyping	*APOE* (ε2, ε3, ε4)	There is no association found between the APOE polymorphism and schizophrenia.	$p > 0.05$
Moberg et al.[13] (2006)	Case-control (olfactory function study)	28 Scz 26 Ctrl	PCR	SNP genotyping	*APOE* (ε2, ε3, ε4)	There is no association between *APOE* and odour identification in the patients.	$p > 0.05$
Kampman et al.[14] (2004)	Case-control	94 Scz 98 Ctrl	RT-PCR	SNP Genotyping	*APOE* (ε2, ε3, ε4)	*APOE* ε3 linked to later age of onset and the *APOE* ε4/ε4 to early onset in schizophrenia.	$p < 0.05$

*Note: Scz = Schizophrenia, Ctrl = Control, GE = Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real time, RFLP = Restriction Fragment Length Polymorphism, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 1: Apolipoprotein E *(APOE)* in Schizophrenia Susceptibility

Ten studies highlight the significance of *APOE* polymorphism and gene expression in the progression of schizophrenia, as detailed in Table III. In an in vitro model study, Ormel et al.,[22] reported no significant differences in *APOE* gene expression in induced microglia-like cells derived from schizophrenia patients. Several other studies focused on *APOE* polymorphisms, particularly the *APOE* ε4 allele associated with schizophrenia vulnerability.[14] Al-Asmary et al.[19] and Tovilla-Zarate et al.,[18] did not find a significant connection between the *APOE* ε4 allele and schizophrenia. Al-Asmary et al.[19] found *APOE* ε2 allele was associated with an increased risk of schizophrenia, whereas the *APOE* ε3 allele was associated with a decreased risk. Meanwhile, Tovilla-Zarate et al.[18] reported that the *APOE* ε3 allele was associated with an increased risk, while the *APOE* ε2 allele was protective against early-onset schizophrenia. A few studies yielded no association between *APOE* alleles and schizophrenia.[13,16,20] Additionally, Kampman et al.,[14] suggested the *APOE* ε3 allele as a protective factor and the *APOE* ε4 allele as a risk factor for schizophrenia. Kecmanović et al.,[15] explored the potential therapeutic response of the *APOE* ε4 allele to typical antipsychotics.

Across the ten studies investigating *APOE* variants, five reported statistically significant results ($p<0.05$), while five found no significant effects (Figure 2). Among the primary studies, three identified increased schizophrenia-related risk susceptibility, including *APOE* ε4-associated structural brain alterations. Two studies reported protective effects linked with the ε2 or ε3 alleles. The remaining studies showed no significant differences in allele or genotype distributions among the schizophrenia and control groups.

Table IV: Classification of articles according to Theme 2

Author (Year)	Study Design	Sample Size (n)	Method	Type of Genetic Analysis	Genes	Key findings	p-value
Shishido et al.[30] (2023)	Case–control (Postmortem brain study)	25 Scz 21 Ctrl	RNA Seq	GE	*APOA (APOA1* and *APOA2)*	*APOA1* is highly expressed in high-stress response schizophrenia	NA
Hwang et al.[29] (2013)	Case-control (Postmortem brain study)	33 Scz 34 Ctrl	RT-PCR	GE	*APOL (APOL1)*	*APOL1* is upregulated in schizophrenia.	p = 0.02
Lee et al.[28] (2013)	GWAS pathway analysis	1378 Scz 1351 Ctrl	ICSN pathway analysis	Functional SNP annotation	*APOL (APOL2)*	*APOL2* was found in schizophrenia.	p < 0.01
Dong et al.[27] (2012)	Case-control (Postmortem brain study)	6 Scz + 6 bip 12 Ctrl	RT-PCR	GE	*APOBEC (APOBEC3A* and *APOBEC3C)*	*APOBEC3A* and *APOBEC3C* are downregulated in the parietal cortex in schizophrenia patients.	p < 0.01
Carrera et al.[25] (2010)	Case-control	301 Scz 604 Ctrl	MALDI-TOF MS	SNP genotyping	*APOL (APOL1)*	No association found between *APOL1* variants and schizophrenia.	p > 0.05
Suzuki et al.[31] (2008)	Case-control	40 Scz (20 Medicated and 20 drug naïve) 40 Ctrl	RT-PCR	GE	*APOER2*	*APOER2* mRNA levels decreased after six months of antipsychotic treatment.	p < 0.01
Takahashi et al.[24] (2008)	Family-based association	377 families	MALDI-TOF MS	SNP genotyping	*APOL (APOL1-6)*	*APOL1,2* and *4* SNPs are significantly involved with schizophrenia.	p < 0.01
Tomita et al.[32] (2007)	Case-control	845 Scz 707 Ctrl	PCR-RFLP	SNP genotyping	*APOL (APOL1-6)*	No significant observations in individual SNPs. The combination of GG genotypes of SNP VI-1 and SNP V-2 is protective against schizophrenia.	p < 0.01
Zhang et al.[23] (2006)	Case-control	424 Scz 473 Ctrl	PCR	SNP genotyping	*APOD*	No association was found between the polymorphism of *APOD* and schizophrenia.	p > 0.05
McGhee et al.[26] (2005)	Case-control (Postmortem brain study)	219 Scz 230 Ctrl	SNaPshot	SNP genotyping	*APOL (APOL1,2* and *4)*	No association was found between the polymorphism of *APOL* family genes and schizophrenia.	p > 0.05

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, RFLP = Restriction Fragment Length Polymorphism, RNA Seq = RNA Sequencing, ICSN = Integrated Candidate SNP Network, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry, SNAPshot = Single Nucleotide Primer Extension

Theme 2: Apolipoprotein-related Genetic and Molecular Interactions in Schizophrenia

Ten studies assessed the primary role of apolipoprotein-related genes in contributing to the pathophysiology of the disorder, as summarised in Table IV. Takahashi et al.,[24] reported significant associations between *APOL* family genes (*APOL1, APOL2*, and *APOL4*) and schizophrenia. Similarly, Hwang et al.,[29] identified *APOL1* as significantly involved in the disorder, while Lee et al.,[28] highlighted the role of *APOL2*. Despite these associations, Carrera et al.[25] and McGhee et al.[26] found no significant association between *APOL* family gene polymorphisms and schizophrenia. Through binomial and random permutation (BRP) statistical analysis on seven SNPs in the *APOL* gene cluster, Tomita et al.,[32] found consistent protective allele or genotype interactions across two independent datasets, although no significant risk factors were identified based on their analysis.

The *APOA1* was upregulated in high-stress response schizophrenia.[30] Additionally, Suzuki et al.,[31] noted a downregulation of *APOER2* mRNA after six months of antipsychotic treatment. Additionally, Dong et al.,[27] found a significant decrease in *APOBEC3A* and *APOBEC3C* gene expression in the parietal cortex of individuals with schizophrenia, suggesting potential alterations in DNA demethylation mechanisms that increase the schizophrenia risk. Zhang et al.,[23] investigated the relationship between *APOD* single-nucleotide polymorphisms (SNPs) and schizophrenia but found no association.

Across the ten studies assessing apolipoprotein-related gene family variants, four reported significant associations with schizophrenia risk, while the remaining studies showed either no association or only trends (Figure 3). Major findings were primarily concentrated in *APOL1, APOL2, APOL4, APOBEC,* and *APOER2,* reporting risk-increasing effects. One study on *APOA* expression demonstrated protective effects on schizophrenia.

Table V: Classification of articles according to Theme 3

Author	Study Design	Sample Size (n)	Method	Type of genetic analysis	Genes	Key findings	p-value
Fan et al.[40] (2021)	Cross-sectional pharmacogenetic	1979 Scz	RT-PCR	SNP genotyping	*APOA (APOA1)*	*APOA1* (rs5072) associated with increased triglyceride (TG) levels in schizophrenia patients treated with combination of antipsychotic drugs.	p = 0.03
Li et al.[42] (2021)	Case-control	301 Scz 156 Ctrl	ARMS-PCR	SNP genotyping	*APOE* (ε4)	*APOE* ε4 associated with hyperlipidaemia and diabetes.	p < 0.05
Li[41] (2021)	Cross-sectional	301 Scz	ARMS-PCR	SNP genotyping	*APOE* (ε2)	*APOE* ε2 genotype associated with lower LDL (low-density lipoprotein) levels.	p < 0.01
Li et al.[39] (2020)	Cross-sectional	301 Scz	ARMS-PCR	SNP genotyping	*APOE* (ε3)	*APOE* ε3 variant associated with higher LDL and hyperlipidaemia.	p = 0.03
Ban et al.[35] (2017)	Cross-sectional	300 Scz	PCR-LDR	SNP genotyping	*APOE* (ε2, ε3, ε4)	*APOE*-ε2 allele associated with lower LDL level and cholesterol.	p < 0.01
Kao et al.[38] (2014)	Prospective 3-month trial	129 Scz	PCR	SNP genotyping	*APOE* (ε4)	*APOE* ε4 is positively correlated with increased TC levels under paliperidone	p < 0.01
Hong et al.[34] (2012)	Cross-sectional pharmacogenetic	466 Scz	MALDI-TOF MS	SNP genotyping	*APOA* (APOA5)	Two alleles of *APOA5* (–1131C and –3G) associated with the increased of TG in the patients treated with risperidone.	p < 0.01
Clark et al.[36] (2009)	Case-control	427 Scz	PCR-RFLP	SNP genotyping	*APOE*	*APOE* variants influenced diabetes under medications.	p = 0.04
Vik-Mo et al.[37] (2009)	In vitro cell culture	4 in vitro cell culture	RT-PCR z	GE	*APOE*	The expression of *APOE* increased in cell culture on treatment with clozapine, olanzapine, haloperidol and imipramine.	p < 0.01
Smith et al.[33] (2008)	Cross-sectional pharmacogenetic	189 Scz	PCR	SNP genotyping	*APOC (APOC3)* and *APOA (APOA5)*	The rare alleles and haplotypes of *APOA5* and *APOC3* genes associated with varied cholesterol and triglyceride levels in patients treated with specific antipsychotics.	p < 0.05

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, RFLP = Restriction Fragment Length Polymorphism, ARMS = Amplification refractory mutation system, LDR= ligase detection reaction, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 3: Apolipoprotein Variations Influence on Lipid Metabolism in Schizophrenia

Table V shows the relationship between apolipoprotein genes and lipid metabolism in individuals with schizophrenia, focusing on lipid profiles, the impact of antipsychotic medications, and the clinical outcomes. The *APOE* ε4 allele was significantly associated with hyperlipidaemia in elderly schizophrenia patients. At the same time, the *APOE* ε3 homozygous genotype was associated with higher concentrations of low-density lipoprotein (LDL) and hyperlipidaemia compared to the heterozygous *APOE* ε3 genotype.[39,42] The *APOE* ε2 allele was discovered to be a protective factor, associated with lower LDL and cholesterol levels in elderly schizophrenia patients.[35,41]

Regarding antipsychotic treatments, a significant upregulation of *APOE* expression was reported.[37] Specifically, Kao et al.,[38] discovered that the *APOE* ε4 is positively correlated with increased TC levels under paliperidone. Similarly, the association between *APOE* variants and cardiovascular risk is pronounced in patients on antipsychotic medication.[36] Additionally, *APOA1* polymorphism has been associated with elevated triglyceride (TG) levels in patients treated with a combination of second-generation antipsychotic drugs (SGAs).[40] Specific variants of *APOA5* (-1131C and -3G) are linked to increased TG in patients on risperidone,[34] while another variant is associated with increased total cholesterol (TC).[33] The specific *APOA5* variant (-1131T/C) affects TC levels depending on the antipsychotic used.[33] Moreover, *APOC3* variants displayed differential impacts of TG levels, whereby the gene variants were associated with reduced TG levels in patients on olanzapine or clozapine. In contrast, other variants are associated with increased TG levels in patients on first-generation antipsychotics (FGAs).[33]

From among the ten studies investigating apolipoprotein gene variants and metabolic effects, one study was excluded,[37] as it did not relate the genetic variants to the lipid profile. One of the studies reported no significant findings, while the remaining eight studies reported statistically significant metabolic associations (Figure 4). Significant findings most commonly involved triglyceride outcomes, where *APOA5, APOC3, APOE* and *APOA1* variants demonstrated metabolically relevant changes. In contrast, several studies reported no triglyceride or cholesterol effects for *APOE* ε2 or ε3 alleles. LDL findings were mixed, with both increases and decreases observed depending on the research and analysis. Protective patterns were observed for the *APOE* ε2 allele.

Table VI: Classification of articles according to Theme 4

Author	Study Design	Sample Size (n)	Method	Genetic Analysis	Genes	Key findings	p-value / CFG score
Rao et al.[51] (2021)	Case-control	637 Scz 467 Ctrl	MALDI-TOF-MS	SNP genotyping	Gene: *APOE* Proteins: *APOA* (APOA1) and APOB	APOA1 and APOB are significantly upregulated with positive cognitive performance and are influenced by the *APOE* (rs429358) polymorphism.	p < 0.01
Jonas et al.[50] (2019)	Longitudinal study	116 Scz	Microarray	SNP genotyping	*APOE* (ε4)	*APOE*-ε4 allele associated with increased escalating psychotic symptoms in late adulthood.	p < 0.01
Vila-Rodriguez et al.[44] (2017)	Case-control	86 Scz 39 Ctrl	RT-PCR	SNP genotyping	*APOE* (ε4)	*APOE*- ε4 allele associated with improved verbal memory.	p < 0.01
Ward et al.[46] (2017)	Cross-sectional pharmacogenetic	122 Scz	RT-PCR	SNP Genotyping	*APOE* (ε2, ε3, ε4)	*APOE*- ε4 allele is linked with poor verbal memory.	p < 0.01
Liebers et al.[52] (2016)	Longitudinal study	8616 Scz	Microarray	SNP genotyping	*APOE* (ε4)	*APOE*- ε4 allele associated with cognitive decline.	p < 0.01
Verbrugghe et al.[43] (2012)	Case-control	336 Scz 172 Ctrl	Microarray and RT-PCR	SNP genotyping and GE	*APOE* and *APOER2*	The downregulation of *APOER2* is linked with cognitive impairment.	p = 0.03
Kurian et al.[49] (2011)	Longitudinal study	31 Scz	Microarray	GE	*APOE*	*APOE* is decreased in high delusion states among schizophrenia.	CFG score 5.5 for delusions biomarker
Boer et al.[48] (2010)	Experimental animal model	10 APOD–/– mice 10 Wildtype (WT) mice	-	None	*APOD*	*APOD* deficiency is associated with decreased density of kainate and AMPA receptors.	p < 0.01
Rapp et al.[53] (2010)	Cross-sectional (Brain postmortem study)	110 Scz	PCR	SNP genotyping	*APOE* (ε4)	*APOE* - ε4 variant associated with dementia severity among schizophrenia patients.	p < 0.01
Hansen et al.[45] (2006)	Case-control	343 Scz 346 Ctrl	RT-PCR	SNP genotyping	*APOD*	*APOD* is associated with poor long-term clinical outcomes.	p = 0.04
Walker et al.[47] (2006)	Experimental animal study	≥100 transgenic flies ≥100 control flies	RT-PCR	GE	*APOD* homologs	*APOD* homologs have a protective effect against behavioural deficits.	p < 0.01

*Note: Scz=Schizophrenia, Ctrl= Control, GE=Gene expression, SNP = Single nucleotide polymorphism, PCR = Polymerase chain reaction, RT = Real-time, MALDI-TOF MS = Matrix Assisted Laser Desorption and Ionisation Time of Flight Mass Spectrometry

Theme 4: Apolipoprotein Variants and Cognitive Functions in Schizophrenia

This theme highlights the role of apolipoprotein genes on cognitive function among patients with schizophrenia (Table VI). Several studies have discovered that *APOE* ε4 is associated with cognitive impairments in adult schizophrenia.[46,50,52,53,55] Furthermore, gene expression studies have shown that *APOE* expression was downregulated in schizophrenia patients during delusional states.[49] Contrary to earlier findings, Vila-Rodriguez et al.,[44] reported that the *APOE* ε4 allele improves cognitive outcomes. Additionally, Rao et al.,[51] emphasised the significant role of *APOE* in the upregulation of APOA1 and APOB proteins, which could potentially contribute to improved cognitive performance.

Research on the *APOD* gene in schizophrenia has yielded contrasting findings. Boer et al.[48] and Walker et al.,[47] identified *APOD* as a potential protective factor against the development of schizophrenia. In contrast, Hansen et al.,[45] found no significant difference between *APOD* expression and schizophrenia, although *APOD* was related to poor long-term cognitive outcomes due to antipsychotic drugs. Additionally, *APOER2* was found to be significantly downregulated in individuals with schizophrenia who exhibit cognitive deficits, indicating the important role of the gene in the modulation of mental functions in this population.[43]

Eleven studies investigating apolipoprotein gene variants and cognitive outcomes, with ten reporting statistically

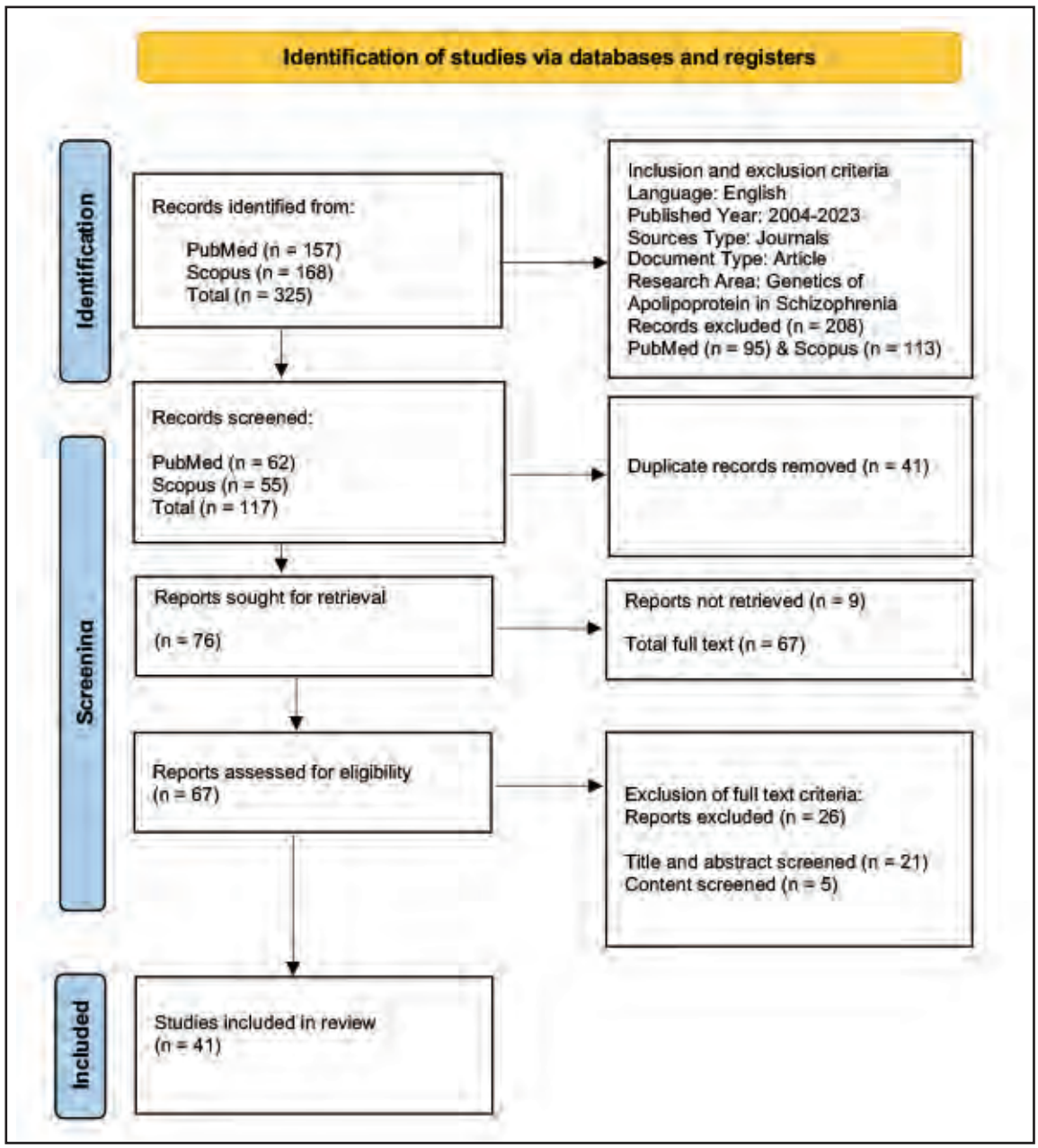

Fig. 1: PRISMA flowchart representing the outline search strategy and outcome of systematic literature review.[12]

significant associations ($p<0.05$) and one showing a trend toward impairment with increased *APOE* expression (Figure 5). The most important findings involved *APOE* ε4, which was associated with poorer cognitive performance across domains such as verbal memory, attention, and dementia severity in multiple studies. *APOER2* downregulation was also implicated in cognitive impairment, while *APOD* variants demonstrated both protective and adverse cognitive associations depending on the study context.

DISCUSSION

Theme 1: Apolipoprotein E *(APOE)* in Schizophrenia Susceptibility

APOE polymorphisms in schizophrenia reveal a complex relationship between different alleles (ε2, ε3, and ε4) and susceptibility to schizophrenia, influenced by their roles in lipid metabolism and neuroinflammation. The ε4 allele is identified as a potential risk associated with modulating brain structure[21] and early-onset schizophrenia,[14] while the ε2 allele is identified as a potential protective factor in schizophrenia.[17,18] These alleles demonstrated various effects due to their efficiency in lipid homeostasis,[56] with the ε2 allele exhibiting the highest efficiency, followed by the ε3 and ε4 allele.[56] Dysregulation in lipid homeostasis leads to lipidation and contributes to neuroinflammation, known to be a factor in the pathophysiology of schizophrenia.[56,57] However, contradictory findings showed that the ε2 and ε3 alleles also contribute to the risk factors of schizophrenia in different populations,[18,19] highlighting the importance of considering genetic and ethnic diversity in the development of schizophrenia. Additionally, several studies could not find an

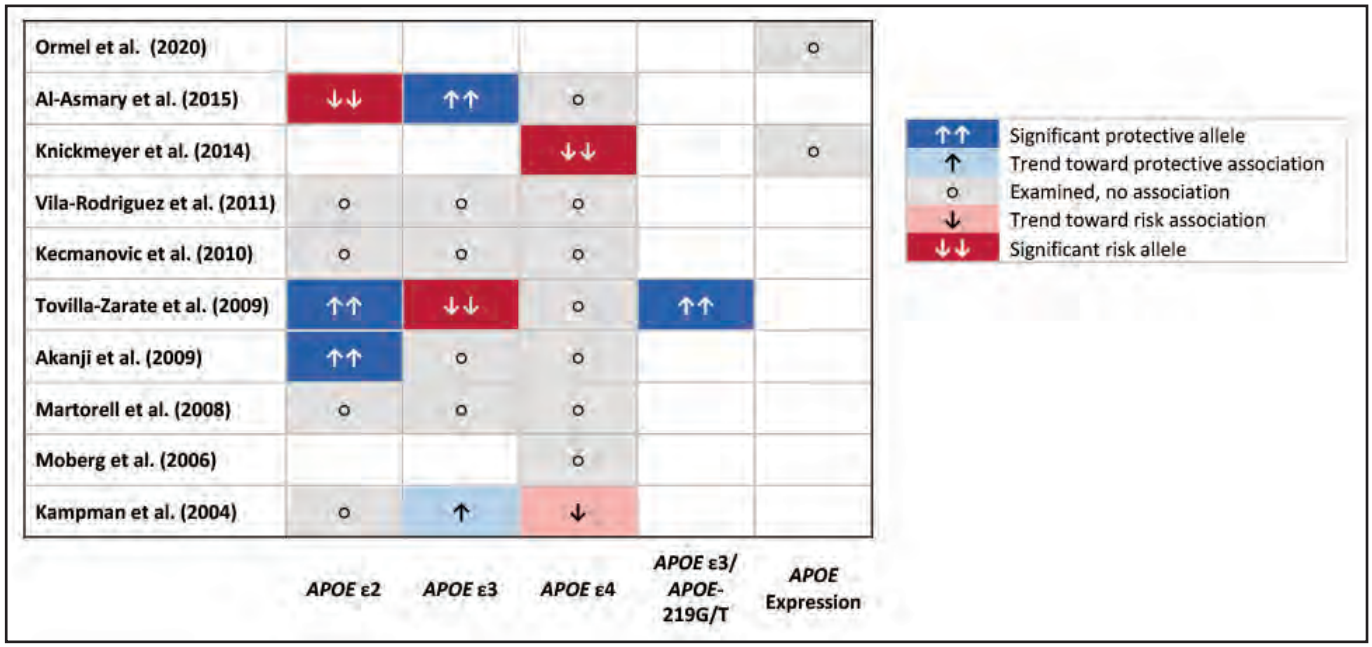

Fig. 2: Heatmap of 10 studies in Theme 1. Risk allele refers to an allele associated with increased schizophrenia susceptibility (higher frequency in cases). Protective allele refers to an allele associated with reduced susceptibility (lower frequency in cases)

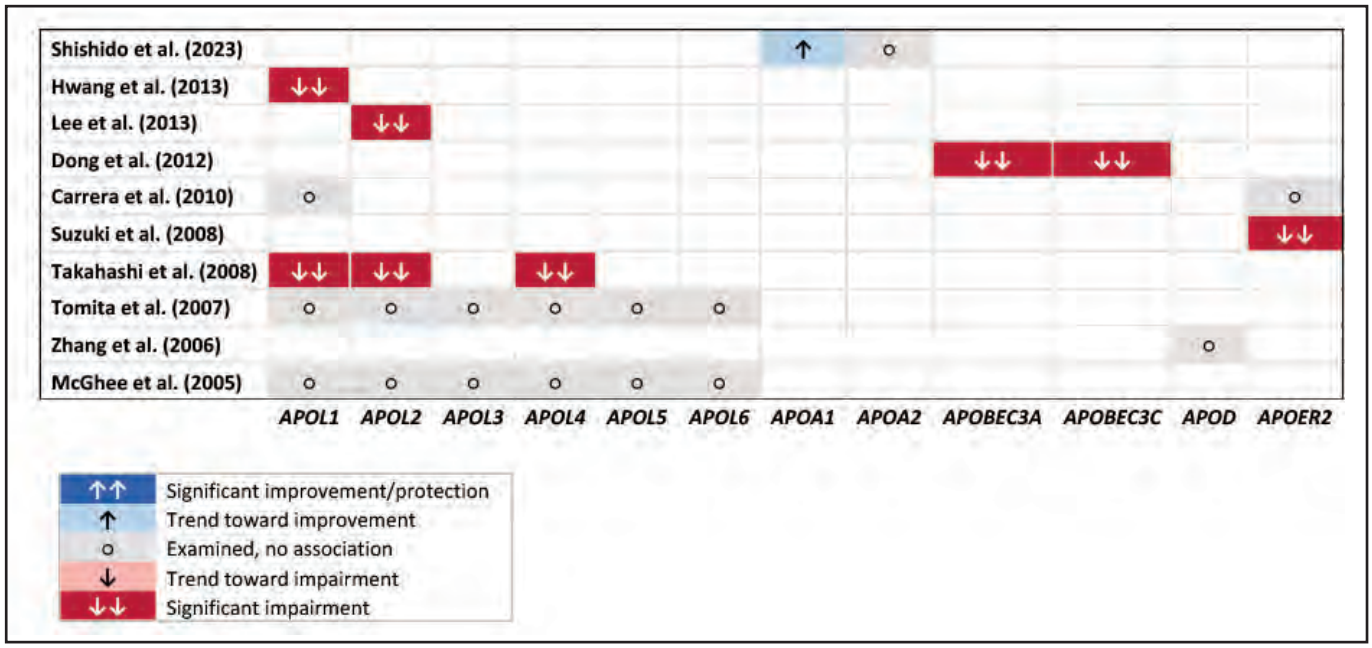

Fig. 3: Heatmap of 10 Studies in Theme 2 showing apolipoprotein-related variants in schizophrenia risk

association between *APOE* variants and the susceptibility to schizophrenia,[16,20] suggesting that *APOE* genes exert a small effect, which requires a large sample size to be significantly detected.[7]

Understanding the cellular and molecular phenotypes in schizophrenia may help generate hypotheses on the potential role of *APOE* expression and neuroinflammation in the disorder's pathogenesis. Microglia play a critical role in neuroinflammation and neurodevelopment, which are important in this context.[58] While *APOE* gene expression in induced microglia-like cells (iMG) showed no difference between schizophrenia patients and controls, mass cytometry revealed a significant upregulation of APOE protein levels in schizophrenia patients.[22] Additionally, iMG derived from schizophrenia showed an increased response to lipopolysaccharide (LPS) stimulation, which leads to the high secretion of pro-inflammatory cytokines TNF-α,[22] highlighting the association of APOE with inflammation. The neuroinflammatory state, driven by activated microglia, contributes to structural brain changes, such as reduced hippocampal volume, in schizophrenia.[59] These observations

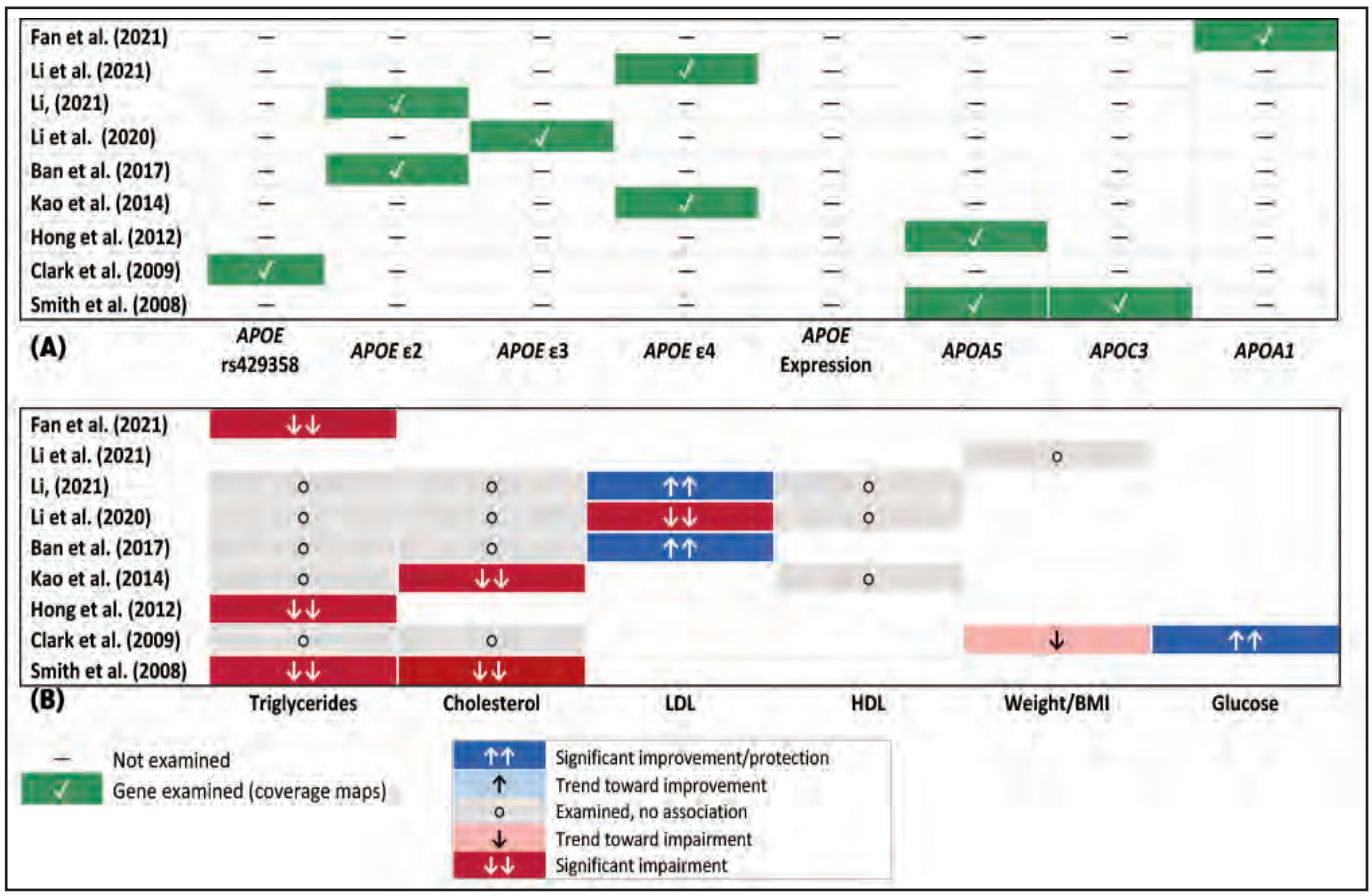

Fig. 4: Heatmap of 9 studies in Theme 3 showing (A) gene coverage and (B) metabolic effects associated with apolipoprotein related variants

suggest a possible link between APOE protein levels, neuroinflammation and schizophrenia-related phenotypes that may contribute to the disorder's pathogenesis.

Antipsychotic medications are commonly used to treat schizophrenia patients, although therapeutic responses vary among individuals.[60] One study suggested an association between the *APOE* ε4 allele and the influence of the first-generation antipsychotics in schizophrenia patients positively,[15] indicating better treatment outcomes for the carriers of this allele. However, different generations of antipsychotic drugs may vary in the mechanism of action, resulting in various adverse effects in patients.[61] This finding highlights the importance of considering the possibility that genetic variations in antipsychotic drug response, reinforcing the value of personalised medicine approaches in psychiatric care.[62]

Apolipoprotein E receptor type 2 (APOER2) is the target for reelin, which is essential for neuronal development and synaptic plasticity.[63] The binding of APOER2 to the reelin facilitates the connection between neurons in brain development.[64] The reduction of *APOER2* may affect neuroinflammatory signalling, leading to less neuronal damage.[65,66] Even though there was no association between *APOER2* mRNA and drug naïve patients, the mRNA level was downregulated after six months of antipsychotic treatments,[31] suggesting the treatment could modulate the expression of *APOER2* and further reduce the neuronal damage. Therefore, *APOER2* may be a potential drug target to address neuroinflammation and schizophrenia severity. However, the long-term effect of medications on the reelin signalling pathway, impairing the synaptic plasticity, requires further investigation.

Theme 2: Apolipoprotein-related genetic and molecular interactions in schizophrenia

Other apolipoprotein-related genes that have been identified to be associated with schizophrenia include *APOL, APOD,* and *APOA*. The *APOL* gene family consists of six genes that have been studied for their potential involvement in schizophrenia, which identified the associations of *APOL1, APOL2,* and *APOL4* with schizophrenia,[24,28,29] which aligns with their previously described pro-apoptotic properties.[67–71] The studies reported that dysregulation of apoptosis could contribute to excessive cell loss and lead to neuroinflammation.[57,72] However, considering the contrasting results reported by Carrera et al.,[25] and McGhee et al.,[26] who found no association between *APOL* family and schizophrenia, highlights the complexity of *APOL* genes. Additionally, the protective effect and the genotype interactions may reduce the severity of the disorder.[32] These findings demonstrate that the involvement of *APOL* genes in schizophrenia remains inconsistent.

APOD is known to participate as a neuroprotector in lipid metabolism and myelin maintenance, which is crucial for brain development.[73] However, the genetic study that explored *APOD* SNPs and schizophrenia failed to find the association in Han Chinese populations, which may be due to factors such as small sample size and methodological approaches.[23] The authors suggested that one methodological approach to address this issue includes the use of family-based association studies to reduce biases by eliminating potential confounding factors.[74] Moreover, an appropriate sample size is crucial in genetic studies, as a small sample size may fail to identify a true association.[75] *APOD* was suggested to have a possible neuroprotective factor, but its genetic association with schizophrenia remains unclear.

Chronic stress influences the progression of schizophrenia,[76] by forming oxidative stress (OS) and reactive oxygen stress (ROS), which activates the release of pro-inflammatory cytokines that exacerbate neuronal damage.[77] *APOA1* is a high-density lipoprotein that plays roles in antioxidant and anti-inflammatory functions.[78] The elevated gene expression of *APOA1* in high-stress response schizophrenia,[30] highlights their interactions with the environment, influencing the pathophysiology of the disorder. Hence, *APOA1* variable expression may have possible interactions with oxidative stress and inflammation pathways in schizophrenia and potentially act as protective factors against the disorder's susceptibility.

Epigenetic mechanisms such as DNA methylation play a vital role in influencing the progression of schizophrenia.[79,80] The downregulation of *APOBEC3A* and *APOBEC3C* in the brains of individuals with schizophrenia suggests potential epigenetic dysregulation.[27] The enzymes involved in DNA demethylation and the reduction may lead to incomplete demethylation,[81] resulting in gene silencing that interferes with the gene activities responsible for regulating brain function.[82–84] Thus, *APOBEC3A* and *APOBEC3C* are essential in regulating the epigenetic mechanism of DNA demethylation, ensuring normal brain function.

Theme 3: Apolipoprotein Variations Influence on Lipid Metabolism in Schizophrenia

Research on the association between *APOE* genes and clinical outcomes in schizophrenia has gained attention, particularly due to their implications for lipid metabolism. The three major alleles of *APOE*, ε2, ε3, and ε4, exert different effects on lipid metabolism.[85–87] The ε2 allele is the most efficient in transporting lipids, followed by ε3 and ε4.[88] The *APOE* ε2 allele has been found to be associated with lower LDL in elderly schizophrenia patients,[35,41] linking with reduced risks of hyperlipidaemia.[89] Its potential protective role may be due to its anti-inflammatory properties and its isoform-specific ability to promote clearance of plasma lipoprotein.[88] Conversely, the *APOE* ε4 increased the risk of hyperlipidaemia and diabetes in elderly schizophrenia patients,[42] suggesting the ε4 variant is susceptible to health complications such as hyperlipidaemia, diabetes mellitus, and cardiovascular disease.[90,91] The specific isoform has been associated with lower cholesterol efflux,[88] which may accumulate LDL in the blood circulation. While the ε2 allele has been suggested as a potentially protective allele and the ε4 allele as potentially a risk allele, the ε3 allele was the most common and is generally considered to be metabolically neutral in lipid metabolism.[56] However, Li et al.,[39] reported that the ε3 homozygotes were linked to higher LDL levels and an increased risk of hyperlipidaemia than the ε3 heterozygotes among individuals with schizophrenia.

Studies have found that *APOE* genetic and environmental factors may interact to modulate lipid metabolism in patients. The environmental factor that may influence *APOE* expression and its lipid metabolism includes antipsychotic drugs.[39] One previous study performed by Vik-Mo et al.,[37] found increased *APOE* expression in patients with schizophrenia treated with FGA (haloperidol), SGA (clozapine and olanzapine), and antidepressant (imipramine). Additionally, specific *APOE* variants were found to be associated with diabetes in patients on antipsychotics,[36]. This suggests that the observed correlation between *APOE* ε4 and elevated TC levels under paliperidone may reflect a gene-drug interaction rather than a simple genetic effect.[38] Thus, *APOE* genes may contribute to the lipid profile and clinical outcomes in schizophrenia, highlighting the importance of considering both genetic and environmental aspects, such as antipsychotic medications, in research.

Studies have demonstrated that apart from *APOE*, the genetic variations of *APOA1, APOA5,* and *APOC3* are also involved in this association. *APOA1* polymorphisms influenced TG levels in schizophrenia patients under combination drug therapy.[40] *APOA5* variants affect TG levels[34] and TC levels in schizophrenia patients treated with FGA and SGA.[33] Similarly, *APOA5* 1131 (T/C) and *APOC3* TG haplotypes were linked to increased TG levels in patients treated with FGA but decreased in those treated with olanzapine or clozapine.[33] In contrast, *APOC3* CC haplotypes have been discovered to be associated with increased TG in patients under olanzapine or clozapine.[33] These findings indicate the importance of genetic screening to identify high-risk individuals for antipsychotic-induced metabolic abnormalities, as apolipoprotein gene variations in regulating lipid metabolism are affected by the type of antipsychotic treatment.[92,93] Hence, personalised treatments in consideration of genetic profile may help to decrease the metabolic side effects in patients on medications.

Theme 4: Apolipoprotein Variants and Cognitive Function in Schizophrenia

Cognitive deficits, including memory deficits, attention issues, and problem-solving difficulties, influence the quality of schizophrenia patients.[94] *APOE* genes were found to be associated with modulating cognitive function in the disorder.[51] The *APOE* ε4 variant showed a decline in cognitive functions of schizophrenia patients,[46,50,52,53] which has been proposed to be due to the poor efficiency of lipid transportation,[95] leading to the disruption of synaptic plasticity, which is crucial for cognitive function.[96] This variant has been associated with increased amyloid-beta levels and plaque formation in the brain, further degraded inhibitory synapses, and cognitive decline.[97,98] In contrast, a study by Vila-Rodriguez et al.,[44] identified that the ε4 allele is involved in cognitive improvement in young schizophrenia patients, suggesting antagonistic pleiotropy. While the *APOE*

ε4 allele was found to be associated with improvement in cognitive abilities among young patients, it is associated with the increased risk of cognitive decline at a later age.[99] Hence, these findings suggest that *APOE* polymorphism may be associated with cognitive outcomes among individuals with schizophrenia.

APOD has been proposed to play a neuroprotective role in relation to cognitive functions in schizophrenia.[47,48] It has been reported to exhibit antioxidant activity, which may help reduce oxidative stress, apoptosis, and neuronal damage in neurodegenerative disorders.[100] While the *APOD* exerts its protective effects, it is involved in the cognitive declines in patients on treatment,[45] suggesting that antipsychotic drugs may dysregulate the *APOD* expression. The dysregulation of *APOD* may unintendedly impact cognitive functions, highlighting the complex interaction between *APOD* and cognitive function in schizophrenia.

The reelin signalling pathway, involving the interaction between reelin and APOER2, is critical in brain development,[101] highlighting the significance of its role in regulating cognitive function.[64,102] Hence, the dysregulation of this pathway, including the decreased expression of *APOER2,* has been reported to be associated with cognitive deficits.[43] The reduction of *APOER2* may influence the synaptic plasticity,[103,104] which could be relevant to the deterioration of cognitive functions.[105] Similarly, APOE interacts with APOER2 in the reelin signalling pathway to maintain synaptic plasticity by supporting membrane homeostasis and repairing injury in the brain.[104] The downregulation of *APOE* associated with high states of delusion in schizophrenia may have relevance for cognitive function.[49] These findings suggest that *APOE* and *APOER2* integrate to maintain the regulation of the reelin signalling pathway, as reduced expression of these genes may contribute to altered synaptic plasticity that has been linked to cognitive differences in schizophrenia.

LIMITATIONS

This review has several limitations. First, it uses only two databases (PubMed and Scopus). Relevant studies indexed in other sources, such as Embase, Web of Science, PsycINFO, and grey literature sources, may not have been included, potentially limiting the comprehensiveness of the evidence base. Variability across study designs, sample characteristics, and biological materials (e.g., blood, plasma, post-mortem brain tissue, and cells) limits direct comparability of results. Analytical methods also differed substantially from PCR-based genotyping to gene expression, introducing further methodological inconsistency. Although the review synthesises progress in genetic studies of apolipoproteins in schizophrenia, several research gaps remain. Most available studies focus mainly on *APOE*; other apolipoprotein genes, such as *APOA, APOD, APOL, APOC, APOER2,* and *APOBEC* families, remain understudied, limiting the understanding of their mechanistic roles and potential as treatment targets. Furthermore, the majority of the studies included are observational; therefore, the associations identified should not be interpreted as causal but rather as requiring validation in longitudinal or experimental investigations.

CONCLUSION

This review investigated the relationship between apolipoprotein genes and schizophrenia across four themes, discussing their roles in susceptibility, genetic interaction, lipid metabolism, and cognitive function. The researchers reported that apolipoprotein genes, particularly *APOE*, associate with the risk of schizophrenia. Additionally, apolipoproteins influence the lipid profile, resulting in metabolic disturbances in individuals with schizophrenia. Moreover, the connection between apolipoprotein genes and cognitive deficits was emphasised, which could assist to identify potential drug targets. Therefore, future research should aim to identify specific genetic biomarkers to enable improved therapeutic interventions in schizophrenia. However, limitations such as understudied genes and a lack of studies exploring biological mechanisms demonstrate the importance of future research to address these gaps. These associations suggest potential biomarker roles, although causality cannot be inferred from the current evidence base.

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Accuracy of diagnostic performance of confocal laser endomicroscopy in characterising pancreatic cysts: A systematic review

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ABSTRACT

Introduction: Pancreatic cystic lesions (PCLs) are becoming more frequently diagnosed due to the improved cross-sectional imaging. Although some of them are harmless, others are malignant in nature, and proper diagnosis is very crucial. This systematised review evaluates the diagnostic effectiveness of nCLE in characterising pancreatic cysts in terms of sensitivity, specificity, diagnostic yield, as well as its strengths versus conventional diagnostic techniques.

Materials and Methods: The systematic literature search was performed in PubMed, Scopus, and Google Scholar, including papers published between 2011 and March 2025. The inclusion criteria were randomised, prospective, and retrospective research in which nCLE diagnostic accuracy was reported in PCLs. Meta-analysis was conducted using PRISMA guidelines for data extraction, risk of bias assessment, and sensitivity analyses.

Results: The inclusion criteria were met in seventeen studies. As shown, nCLE was usually superior to cytology, cyst fluid carcinoembryonic antigen (CEA), and traditional EUS-FNA. Sensitivity was reported to be between 59-98% and specificity is between 82-100%. Of seven studies (n=216 cases) analysed by meta-analysis, the pooled sensitivity was 0.89 (fixed-effects) and 0.88 (random-effects), the heterogeneity was high (I2=74%). The Funnel plot analysis identified the possibility of publication bias and small-study effects. Robustness was ensured through sensitivity analysis, which was always pooled between 0.86-0.92.

Conclusion: It has been noted that nCLE improves diagnostic confidence, reduces indeterminate results, and has the potential to positively influence the economy and clinical management. The current evidence is strongly in favour of the clinical utility of nCLE, more large-scale, multi-centred, and methodologically sound trials are necessary to determine the diagnostic performance of the technique, develop standardised protocols, and evaluate long-term effects on patient outcomes and healthcare systems.

KEYWORDS:
Confocal; Diagnosis; Pancreatic Cyst; Endoscopic ultrasound-guided fine-needle aspiration

INTRODUCTION

Pancreatic cystic lesions (PCL) are progressively identified, with an occurrence of 2.1% to 2.6%. PCL is diagnosed frequently because of the growing use of magnetic resonance imaging (MRI) and computed tomography scans (CT scans).[1,2] Pancreatic cystic lesions (PCL) are progressively identified, with an occurrence of 2.1% to 2.6%. PCLs need careful assessment due to their potential for malignancy.[3] By determining the presence of high-risk features and utilising cutting-edge technologies like needle-based confocal laser endomicroscopy (nCLE) and molecular markers, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and laboratory techniques, optimal surveillance can be achieved by balancing the risk of pancreatic cancer mortality against cost and surveillance burden. Surgical removal is recommended for lesions with malignant potential, including cystic neuroendocrine neoplasms, mucinous cystadenomas and branch duct intraductal papillary mucinous neoplasms (BD-IPMNs).[4]

Current imaging techniques are not optimal for determining their malignant potential. Inaccurate diagnoses could lead to missed lesions or unnecessary surgery.[5] Presently, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with cystic fluid examination remains the most effective nonsurgical approach for detecting the characteristics of PCLs.[6,7] However, Thornton et al.,7 demonstrated cytology has low sensitivity but has good specificity whereas Napoleón et al.,8 argued cytology can achieve up to 60% of sensitivity for malignancy while maintaining high specificity. Cyst fluid carcinoembryonic antigen (CEA) with a threshold of 192ng/ml, is recognised as a more accurate diagnostic indicator as compared to cytology and EUS for distinguishing non-mucinous and mucinous PCLs.[6] In contrast, van der Waaij et al.,[9] identified low levels of CEA as a specific biomarker for distinguishing between benign and premalignant cysts. Nonetheless, the diagnostic limitations of these techniques resulted in suboptimal management of patients, possibly leading to excessive repetitive surgical interventions and follow-ups.[10,11] Implications are crucial, impacting patients by leading to higher mortality and morbidity rates and also imposing a financial burden on the healthcare system because of ineffective interventions.[12,13]

Needle-based confocal laser endomicroscopy (nCLE) is a cutting-edge imaging technique that allows in vivo, real-time

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microscopic examination of the inner wall of a pancreatic cyst during an EUS-FNA process.[14] Konda et al.,[15] demonstrated the safety and feasibility of nCLE for the evaluation of PCLs and its accuracy was proven in an international multicentre study.[16] Subsequent studies investigated a nexus between histological characteristics and nCLE imaging, leading to the development of standardised nCLE criteria for distinguishing the most common types of PCLs.[17,18] Napoléon et al.,[19] conducted a CONTACT2 clinical trial that prospectively demonstrated the high sensitivity and specificity of nCLE for diagnosing PCLs in a large multicentre cohort of 78 cases with confirmed surgical or cytohistological diagnoses. Therefore, this review aims to comprehensively summarise and critically analyse the existing literature on the diagnostic performance of confocal laser endomicroscopy (CLE), specifically evaluating its sensitivity and specificity in detecting pancreatic cyst lesions. Moreover, this review investigates the efficacy of nCLE in the characterisation of pancreatic cyst lesions and its possible role as a promising diagnostic approach for PCL.

MATERIALS AND METHODS

This review was conducted following the methodological framework of a systematic literature review, adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1).

Search strategy

PubMed/MEDLINE, Scopus and Google Scholar (electronic databases) were searched systematically from January 1, 2011, to March 31, 2025. The search used a strategy combining Medical Subject Headings (MeSH) and free-text terms, with the help of Boolean operators (AND, OR), to retrieve as many relevant studies as possible. diagnostic. Filters were used to reduce the results to human studies, English language and 2011 or later publications, which are approximately the time of introduction of nCLE in pancreatic imaging. In addition to database searches, the reference lists of the included studies were searched to identify further eligible records.

Inclusion criteria

This review included studies during the period 2011-2024, particularly focusing on the diagnosis of pancreatic cysts with confocal laser endomicroscopy, which were considered eligible. The studies that incorporated needle-based confocal laser endomicroscopy as a diagnostic process for treating illnesses other than pancreatic cysts, as well as those that did not discuss cysts in pancreatic diagnosis, and the sensitivity of the diagnosis were also excluded.

Data collection and preparation

After screening the eligible studies that met the specified criteria, studies were documented in Google Sheets. Each article was then reviewed individually and its relevance was approved for inclusion.

RESULTS

Study selection

A total of 351 studies were extracted from databases from between the years 2011 and 2024, of which 183 studies were found relevant to the review's aim after the removal of duplication. The following studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). After appropriate screening of the data based on title, abstract, and keywords, 43 studies were removed. Further exclusion of studies was based on the following reasons: needle-based confocal laser endomicroscopy used for diagnosing conditions beyond pancreatic cysts (n=45), didn't discuss cyst in pancreatic diagnosis (n=22), non-English language (n=19), and non-human subject (n=18). Thus, 21 studies were considered for inclusion.[14-35]

Risk of bias assessment

All eligible studies were evaluated using a standardised risk-of-bias tool to conduct a quality appraisal. In this review, the studies were critically reviewed on methodological rigour such as patient selection and outcomes and transparency of reporting. Reports that were considered to have a serious risk of bias, including incomplete outcome reporting, unclear diagnostic reference standards, or serious methodological limitations, were excluded from the final synthesis to preserve the integrity of the review. Consequently, only studies with low to moderate risk of bias were retained, and thus the findings presented can be considered evidence of better methodological quality. This process of exclusion enhances the consistency of our combined findings and removes the risks of inaccurate or biased information, and gives more confidence to the estimates made on diagnostic accuracy in needle-based confocal laser endomicroscopy characterisation of pancreatic cysts.

Study characteristics

Seventeen studies were included in the systematic review after risk of bias assessment, the clinical and safety of needle-based confocal laser endomicroscopy (nCLE) in pancreatic cystic lesions (PCLs) have been addressed in a variety of study designs, including initial pilot studies, large prospective multicentre trials and meta-analyses. Pilot studies by Konda et al.,[15,16] have indicated that nCLE imaging was technically feasible in 17/18 EUS-FNA cases, with their former pilot study indicating that it was highly specific, almost 100% to detect pancreatic cystic neoplasia, although sensitivity was low (59%).[15] Expanding on this, Napoléon et al.,[19] stated that nCLE was accurate in diagnosing serous cystadenoma (87%), with a sensitivity value of 69% and a specificity value of 100% and can be used to differentiate between benign and malignant lesions. These findings have since been confirmed in other large-scale studies done by several single-centre and multicentre prospective and retrospective studies. As an illustration, Chin et al.[20] found 83.3% sensitivity, 75% specificity, and Krishna et al.[21] reported high diagnostic quality (sensitivity 94%, specificity 82%, accuracy 89%), with nCLE having demonstrated a great potential in the recognition of characteristic imaging patterns. Moreover, Cheeseman et al.,[22] emphasised that nCLE, as well as microforceps biopsy, had a high diagnostic yield (84.1% and 34.1% with cyst fluid cytology, respectively). Feng et al.,[23] added to these results by reporting accuracy of 94%, specificity of 100 %, and sensitivity of 75% in the detection of malignant mucinous cysts, but reported adverse events, including pancreatitis, bleeding, perforation, and infection. Similarly, Hao et al.,[24] noted high diagnostic values of

pancreatic ductal adenocarcinoma at an accuracy of 90% and sensitivity of 90.3%. Multicentre and large-scale analysis is another source of evidence of the clinical usefulness of nCLE. In a multicentre prospective cohort of 206 patients, Napoléon et al.,[19] showed outstanding diagnoses of different types of pancreatic cysts with sensitivity and specificity of over 95% versus EUS and cyst-fluid CEA. Similarly, Krishna et al.,[25] demonstrated that EUS-nCLE had a better diagnostic accuracy 97% in differentiating between mucinous and non-mucinous PCLs as compared to the conventional cytology and CEA. This was also confirmed by Machicado et al.,[26] who reported that nCLE had a high diagnostic accuracy in non-mucinous cysts and a moderate accuracy in mucinous lesions, and their follow-up systematic training study Machicado et al.,[27] showed that endosonographers with low experience could be reliably trained to reach a diagnostic accuracy 82-96%. There have also been economic and management implications. According to Le Pen et al.,[28] the combination of EUS-FNA and nCLE yielded a high level of diagnostic (sensitivity 69%, specificity 100%) performance, which was not only better than EUS-FNA alone (sensitivity 20%, specificity 90%), but was also more cost-effective. In the same vein, Palazzo et al.,[14] showed that the combination of EUS-nCLE-FNA resulted in an increase of BD-IPMNs diagnosis by 48 to 65 cases and the decrease of indeterminate mucinous cysts by 35 to 16 cases, indicating its clinical practice-refining ability.

Adverse events (AEs) were typically rare and controllable in studies. During this time, individual reports reported pancreatitis[15,21,23] and bleeding, infection, and perforation[23,19] whereas large systematic reviews found AE rates of 2.6-6.6% on overall.[29] The two meta-analyses that are included in the review showed high pooled diagnostic performance with sensitivities of 83-98% and specificities of 82-100%. The sensitivity and specificity of nCLE shown by Wang et al.30 were presented with pooled sensitivity of 90% and a specificity of 96%, with an AUC of 0.94, which confirms high reliability of nCLE.

Meta-Analysis

Forest Plot

Forest plot shows the sensitivity of a diagnostic test in seven studies that were done between 2013 and 2018 and as a group assessed 216 cases of disease, with each study in the estimation of sensitivity ranging between 0.59 and 0.94 (Figure 2). Konda et al.,[16] reported a sensitivity of 0.59 (95% CI: 0.36, 0.79) based on 22 cases, and Napoléon et al.,[17] reported a sensitivity of 0.69 (95% CI: 0.39, 0.91) based on 13 cases; both indicate moderate performance with wide CIs. Conversely, Krishna et al.,[18] found 0.94 (95% CI: 0.71, 1.00) in 17 cases, Chin et al.,[20] 0.83 (95% CI: 0.36, 1.00) in six cases, Krishna et al.,[21] 0.88 (95% CI: 0.73, 0.96) in 40 cases and Hao et al.[24] The sensitivity pooled under a fixed-effects model is 0.89 (95% CI: 0.84, 0.92) and random-effects model, which controls the heterogeneity (I2 =74.0, t2 =0.837, p=0.0008) is 0.88 (95% CI: 0.72, 0.96), meaning that it can detect the presence with high sensitivity with certain variability. The high heterogeneity implies perhaps a difference in study design or population, which means that clinical generalisability should be based on the random effects estimate. This defines its pooled sensitivity as a useful tool for reliably ruling out testing, but clinicians need to pay attention to specificity measures and circumstances-specific results, and subsequent studies to respond to heterogeneity by utilising standardised procedures and larger studies.

Funnel Plot

The meta-analysis of seven studies sensitivity funnel plot shows the evaluation of the publication bias and the heterogeneity of studies with sensitivity estimates versus the standard errors of these estimates (Figure 3). Studies by Konda et al.,[16] Napoléon et al.,[17] Krishna et al.,[18] Chin et al.,[20] Krishna et al.,[21] Napoléon et al.,[19] and Hao et al.,[24] are included in the plot with the different coloured markers on a 95% confidence interval funnel. Preferably, the data points must symmetrically be distributed throughout the funnel, with the smaller studies (greater standard errors) being more scattered and the larger studies (lesser standard errors) being around the pooled estimate. In this instance, there was an asymmetry in the plot, where Chin et al.[20] and Napoléon et al.,[15] with sensitivities of 0.83 and 0.69, respectively and greater standard errors (about 0.15) are above the lower boundary of the funnel, which may be underestimated or smaller sample bias. On the contrary, the larger studies, such as those of Hao et al.[24] and Krishna et al.[21], which have sensitivities of 0.94 and 0.88 and smaller standard errors (approximately 0.05-0.075), are more centred and are therefore stable. This asymmetry, especially the skewing of the smaller studies towards the left, can be due to publication bias, where the lower the sensitivity of a study, the higher its probability of publication/inclusion, which can bias the pooled estimate of 0.88 (random-effects model) downward. This implies that the test was sensitive in general, but the findings must be treated with caution, and an attempt to get access to unpublished data or study quality needs to be investigated so that you can establish the strength of these results in regard to your study.

Sensitivity Analysis

The sensitivity analysis of the meta-analysis of diagnostic test sensitivity (Figure 4), included seven studies published from 2013 to 2020 and 216 total diseased cases (leave-one-out, LOO), uses sensitivity analysis by dropping each study and re-estimating the effect size, quantifiers of heterogeneity (t2; I2), and additional p-values of the Cochran Q test. This method determines potential studies that overvalue your overall synthesis and gives an insight on the stability of the findings. Inclusion of Konda et al.[16] also provided a lower sensitivity of 0.59 based on 22 cases, so inclusion in the meta-analysis results in increasing the pooled estimate to 0.92 (95% CI: 0.82, 0.97) and the degree of heterogeneity decreases (t2=0.041, I2=34, p=0.1610) indicating this early study with moderate performance and increased uncertainty as a pull-down on the overall sensitivity and inclusion Likewise, without Napoléon et al.,[17] which has a sensitivity of 0.69 on 13 cases, gives a pooled value of 0.90 (95% CI: 0.73-0.97; t2=0.049, I2=43%), p=0.1670), has moderate effects on the overall value, but the heterogeneity was still significant but not quite as high as with the overall model (I2=74%). Inclusion of Krishna et al.,[18] which is a high-performer with17 cases, leads the result to 0.87 (95%, CI 0.66-0.96; t2=0.094, I2=77%, p=0.0896), although a higher I2 indicates greater

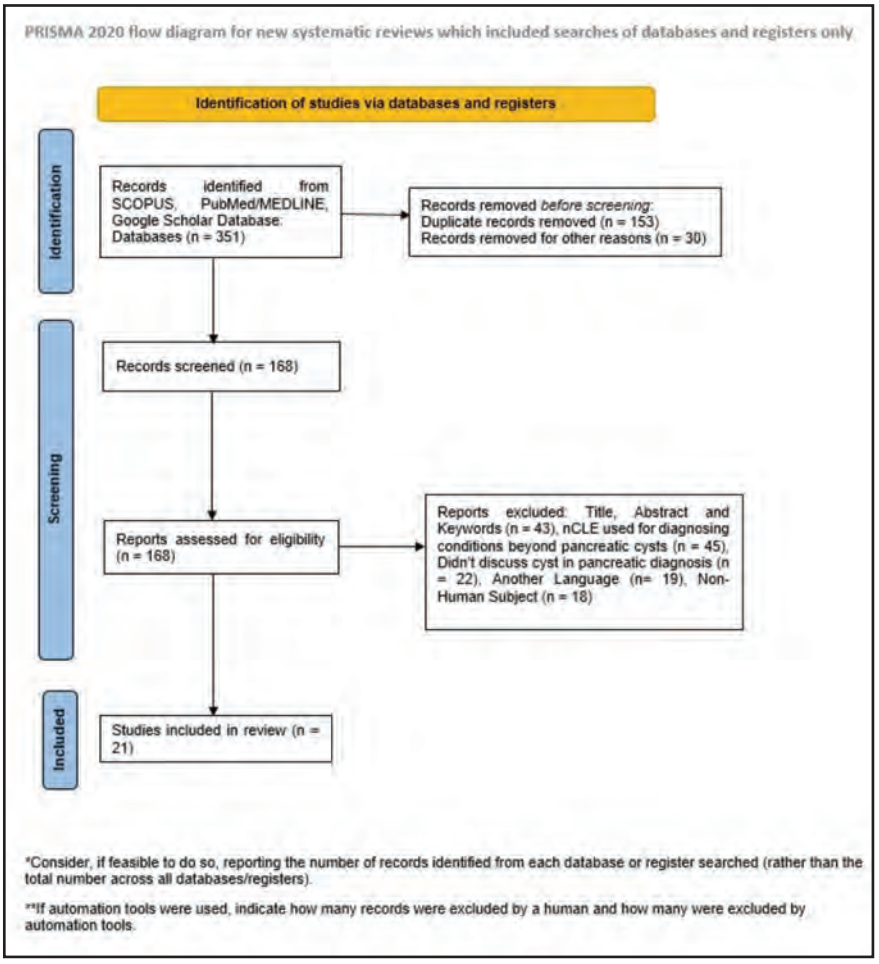

Fig. 1: PRISMA flow diagram

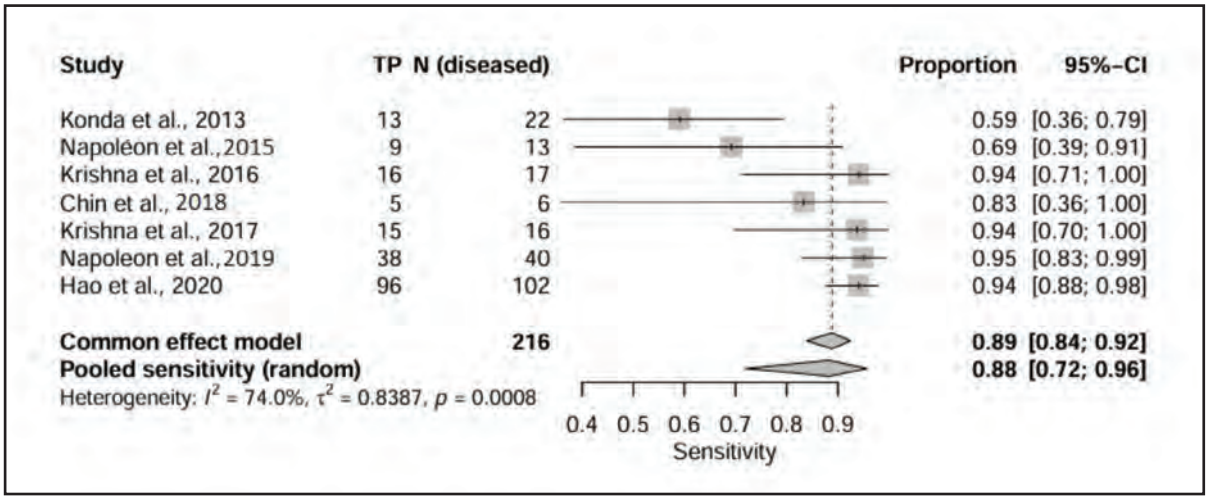

Fig. 2: Forest Plot

spread among the other studies, and thus the stabilising influence of this middle participant. The data are excluded on such a fine line (0.83 representing six cases) to include the Chin et al.,[20] study as the smallest (thus, the CI value represents the minimum possible values), but with a tremendously high heterogeneity I2=73%, indicating the contribution of such underpowered studies rather than a significant shift in the central tendency. The exclusion of Krishna et al.,[21] with a sensitivity of 0.88 on 40 cases reduces the pool to 0.87 (95% CI: 0.65, 0.96; t2=0.099, I2=67%, p=0.0918), indicating that it plays a moderating role in balancing the extremes of both low- and high-sensitivity

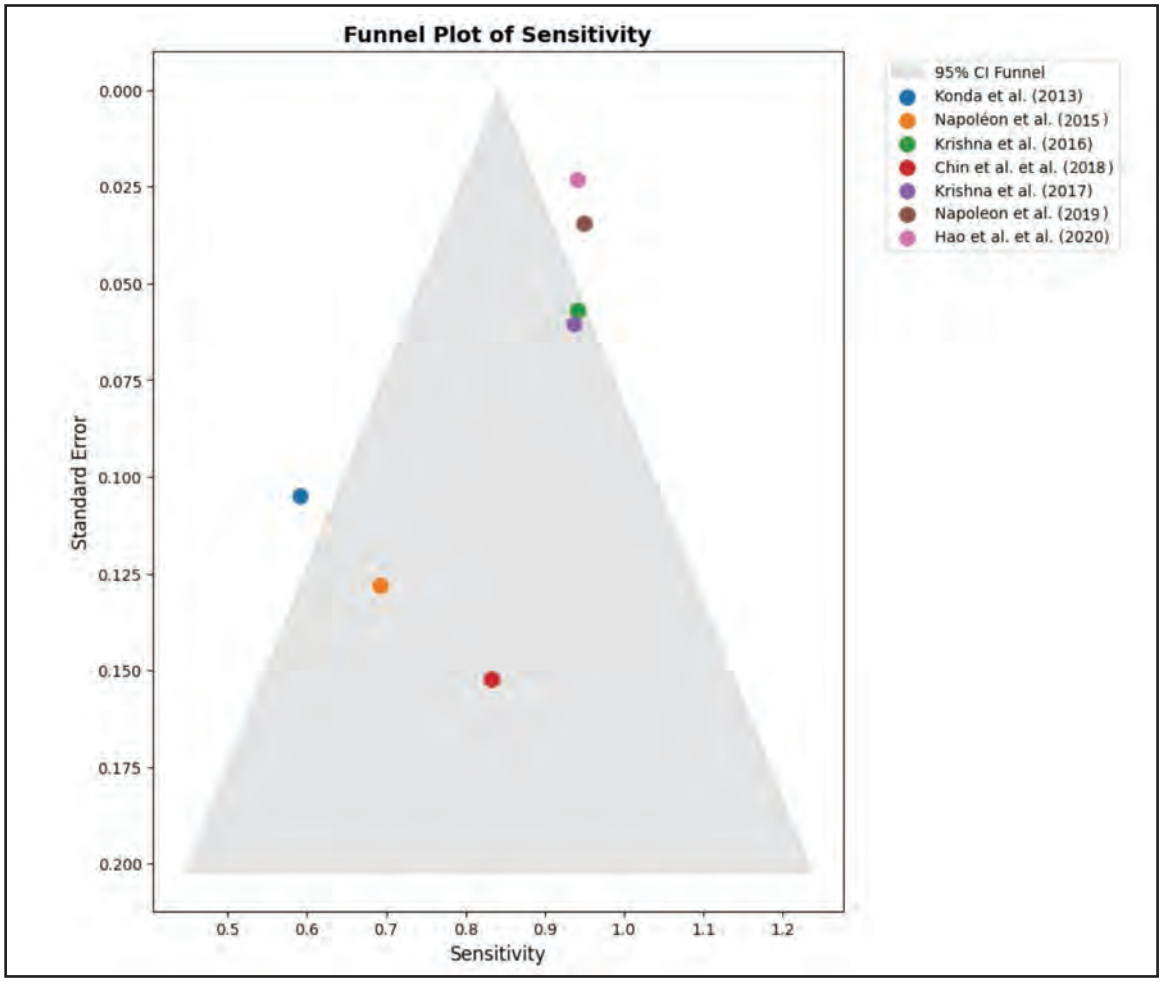

Fig. 3: Funnel Plot

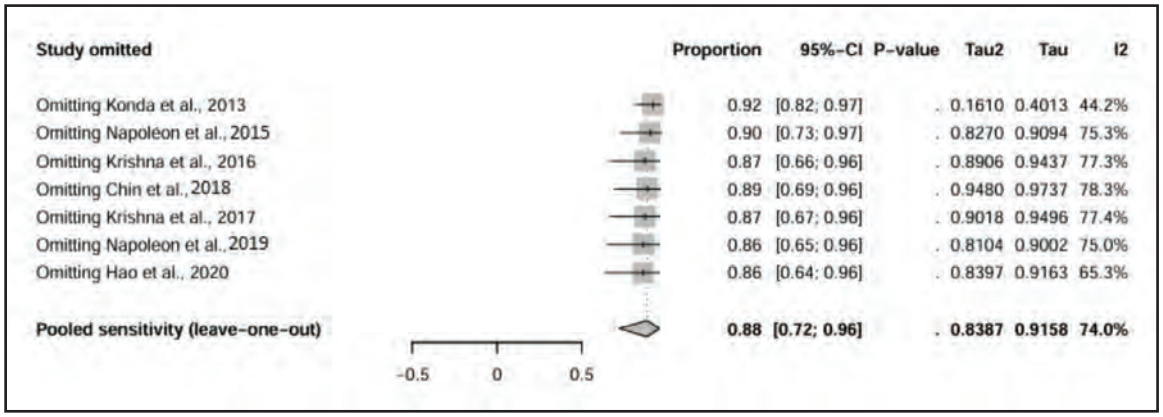

Fig. 4: Sensitivity Analysis

studies. Lastly, Omitting the largest study, Hao et al.[24] (0.94 of 102 cases) results in 0.86 (95% CI: 0.64-0.96; t2=0.116, I2=65%, p=0.0910), which is a slight decrease but still with a greater impact of this strong study, and the t2 value is slightly greater, which confirms the high-weight contribution of this strong dataset In all the LOO iterations, the pooled estimates appear clustering around 0.86-0.92, with CIs equalising the original (not very sensitive to the removal of a single study) and p-values above 0.05 (which means that the meta-analysis is very stable, and none of the results is influenced by a single study). The moderate-to-high persistence of I2 (34%-77) in the majority of situations validates the use of random-effects modelling and additional investigation of heterogeneity sources, but the range of changes is not as wide as it warrants the use of the 0.88 pooled sensitivity as a rule-out criterion in clinical use of your study setting, indicating the high performance of the diagnostic test is not an artifact of individual contributors.

DISCUSSION

The analysis of the study was performed through a systematic review employing different databases to retrieve potential studies. It is crucial to evaluate and identify the risks of PCLs for shaping effective management techniques, considering the high morbidity rate of pancreatic surgery. Our findings suggest that nCLE demonstrates high diagnostic performance in characterising pancreatic cyst lesions and outperforms conventional diagnostic methods. These results were supported by Feng et al.,[23] who identified an accuracy of 94% and a specificity of 100%. In a similar vein, Krishna et al.,[25] observed 94% specificity, 98% sensitivity, and an overall accuracy of 97%, emphasising superior diagnostic performance of nCLE than conventional diagnostic techniques of PCLs. Machicado et al.,[26] indicated that nCLE is predominantly effective in diagnosing non-mucinous cysts and relatively less accurate for mucinous lesions. In addition, Hao et al.,[24] and Napolean et al.,[19] also advocated that nCLE can improve the diagnosis of indeterminate cysts and pancreatic serous cystadenoma, respectively.

Krishna et al.,[25] found EUS-nCLE was more accurately in diagnosing mucinous PCLs in comparison to CEA measurement and cytology analysis. Le Pan et al.,[28] revealed that EUS-FNA alone had a sensitivity of only 20%, while sensitivity reached 69% when nCLE was combined with EUS-FNA, highlighting the enhanced accuracy and drop-in misdiagnosis rate. Cheeseman et al.,[22] revealed that nCLE and MFB substantially improved the accurate detection of PCL as compared to composite standards. Recent high-quality studies through meta-analytical methods support these findings. Systematic reviews by Chin et al.,[29] revealed pancreatic cystic lesion assessments using nCLE showed opposing sensitivity outcomes (59-98%) and specificity (82-100%) and accuracy (71-99%) while confirming nCLE potential as an additional diagnostic method. Due to diverse study designs, studies were unable to determine aggregate diagnostic value statistics. Although improved accuracy with nCLE shows potential for lower unnecessary surgeries Chin et al.,[29] said the high cost of equipment and difficult learning curve for operators prevent widespread adoption. In their meta-analysis Wang et al.,[30] combined 10 studies with 547 patients to establish nCLE's diagnostic abilities through a pooled sensitivity of 90%, a specificity of 96% and an area under the curve (AUC) of 0.94, which demonstrated excellent diagnostic performance. The procedure produced a moderate adverse event rate of 6.6%, consisting of pancreatitis and intracystic bleeding, and mild pruritus cases. The analysis faced limitations from moderate-to-high heterogeneity combined with potential publication biases. The authors emphasised the importance of conducting multicentre trials at scale to achieve validation of these findings in standard clinical practice settings.[30] Bertani et al.[31] reported a diagnostic accuracy of 84%, a sensitivity of 80 %, and a specificity of 100 %, emphasising that EUS-nCLE has proven to be a better performer than standard EUS-FNA. Robles-Medranda et al.[32] demonstrated that the combined nCLE and EUS-guided MFB improves the identification of PCLs with potential malignancy. Konda et al.[16] also advocated the adoption of nCLE with EUS-FNA due to its high diagnostic accuracy. Furthermore, Konda et al.[15] evaluated the safety and feasibility of nCLE in clinical settings and concluded that nCLE is technically feasible in most of the pancreatic EUS-FNA cases. A multi-centre prospective study conducted by Machicado et al.,[27] reveals that a well-designed educational program plays an important role in enhancing the diagnostic accuracy of nCLE. This highlights the significance of standardised training for endo-sonographers to optimise the clinical benefits of nCLE.

The findings demonstrate nCLE provides superior diagnostics compared to conventional methods. Standard diagnostic algorithms can integrate nCLE techniques because of their low rate of adverse incident reports and potential to enhance EUS-FNA results while exposing minimal patient risk.

CONCLUSION

It has been noted that nCLE improves diagnostic confidence, decreases the indeterminate results and has the potential to positively influence the economy and clinical management. Negative occurrences, including pancreatitis, bleeding, and infection, have been mentioned, but these are relatively few and can be overcome, which can convict in the safety of this procedure. The effects of the learning curve and dependence on the operator were rarely considered but might be a dominant factor related to the diagnostic accuracy and reproducibility. With these limitations in consideration, the current evidence is strongly in favour of the clinical utility of nCLE, more large-scale, multi-centred, and methodologically sound trials are necessary to determine the diagnostic performance of the technique, develop standardised protocols, and evaluate long-term effects on patient outcomes and healthcare systems.

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SHORT COMMUNICATION

Diagnostic yield of CTPA and Wells Score utilization in pulmonary embolism assessment: Experience from a Malaysian tertiary hospital

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ABSTRACT

Introduction: Computed Tomography Pulmonary Angiography (CTPA) is the gold standard for diagnosing pulmonary embolism (PE), though concerns about overuse persist.

Materials and Methods: This study evaluated CTPA yield and Wells Score use in 361 adults at a Malaysian tertiary centre (May 2017–July 2021).

Results: PE was confirmed in 29.6% of cases, above international benchmarks. While the Wells Score was applied in 78.5% of cases, only 32.1% adhered strictly to local guidelines.

Conclusion: CTPA was not overutilized, but there is a gap between recommended clinical pathways and real-world decision-making, highlighting the need to standardize practice to improve diagnostic efficiency and support evidence-based care.

KEYWORDS:
Pulmonary embolism; Computed Tomography; Wells Score; Clinical decision rule; Diagnostic yield

INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening condition that requires prompt and accurate diagnosis. Computed Tomography (CTPA) is widely accepted as the gold standard for diagnosing PE due to its high sensitivity, specificity, and accessibility.[1] However, its increasing use has raised concerns about overutilization, with reported diagnostic yields as low as 10% in some centres.[2] To address this, clinical decision rules such as the Wells Score, have been developed to stratify patients based on their pretest probability of PE.[3,4] These tools help determine the need for imaging, particularly when used with D-dimer testing. Despite recommendations to use the Wells Score, inconsistent adherence remains a problem, leading to unnecessary imaging and patient risk.[5] In Malaysia, limited evidence exists on real-world adherence to these tools. This study assesses the utilization of the Wells Score and the diagnostic yield of CTPA at a tertiary centre on the east coast of Malaysia.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cross-sectional study was conducted at Sultan Ahmad Shah Medical Centre @ IIUM (SASMEC @ IIUM), a tertiary teaching hospital in Kuantan, Malaysia. All adult patients (≥18 years) who underwent CTPA between May 2017 and July 2021 were included. Exclusion criteria were previous PE, indeterminate imaging, or CTPA for non-PE indications.

Data Collection

Patient data were obtained from the Radiology Information System and electronic medical records. The Wells Score was retrospectively assigned based on documented symptoms, clinical signs, and risk factors. Patients were stratified into "PE likely" (score >4) and "PE unlikely" (score ≤4) groups. D-dimer results were also collected.

Statistical Analysis

Analysis was conducted using SPSS version 25 (IBM Corp., Armonk, NY). Descriptive statistics summarized demographics and outcomes. Chi-square tests assessed categorical variable associations, and binary logistic regression examined the link between Wells Score and PE diagnosis. A p-value < 0.05 was considered statistically significant.

Ethics Approval

Approval was obtained from the IIUM Research Ethics Committee (Ref: IIUM/305/20/4/1/7, 23 June 2020).

RESULTS

Demographic Characteristics

Out of 366 patients, 361 were included after exclusions. The mean age was 60 years (range 15–92), with 53.2% being female. PE was confirmed in 107 patients, resulting in a 29.6% diagnostic yield. Patient demographics, Wells score stratification, and D-dimer results are summarized in Table I.
Wells Score Stratification

Of the patients, 231 (64.0%) were classified as "PE likely," and 130 (36.0%) as "PE unlikely." Among the "PE likely" group, 33.8% had confirmed PE, compared to 27.1% in the "PE unlikely" group.

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Table I: Demographic, Wells score, and D-dimer characteristics of patients with and without pulmonary embolism (n = 361)

Variable	All patients n (%)	PE patients n (%)	Non-PE patients n (%)
Age group			
<35 years	26 (7.2)	4 (15.4)	22 (84.6)
36–64 years	169 (46.8)	51 (30.2)	118 (69.8)
>65 years	166 (46.0)	52 (31.3)	114 (68.7)
Sex			
Male	169 (46.8)	47 (27.8)	122 (72.2)
Female	192 (53.2)	60 (31.3)	132 (68.7)
Wells score group			
PE likely (>4)	231 (64.0)	78 (33.8)	153 (66.2)
PE unlikely (≤4)	130 (36.0)	29 (22.3)	101 (77.7)
D-dimer result			
Normal	42 (11.6)	14 (13.1)	28 (11.0)
Elevated	198 (54.8)	58 (54.2)	140 (55.1)
Not done	121 (33.5)	35 (32.7)	86 (33.9)

PE, pulmonary embolism.

Table II: Association between Patient Gender, PE Symptoms and Wells Criteria, With PE Result

Variable	p-Value	95 % Confidence Interval	Odd Ratio
Patient demographic			
Gender	0.475	0.538 – 1.335	0.8
PE sign and symptoms			
Shortness of breath	0.028	1.057 – 2.874	1.7
Chest pain	0.660	0.336 – 1.998	0.2
Hemoptysis	0.928	0.318 – 3.510	1.0
Wells Criteria			
Heart rate > 100 beats/min	0.180	0.466 – 1.155	0.7
Clinical sign and symptoms of DVT	0.589	0.503 – 3.349	1.3
Recent surgery or immobilization	0.278	0.809 – 2.083	1.3
History of DVT or PE	0.623	0.337 – 6.121	1.4

PE, pulmonary embolism. DVT, Deep vein thrombosis

Table III: Binary Logistic Regression for the Entire Wells Scores and Patient's Age

Variable	CTPA results		
	PE positive vs. PE negative		
	p-Value	Odd Ratio	95 % Confidence Interval
Wells Score (PE – likely)	0.038	1.149	1.008 – 1.311
Age	0.111	1.013	0.997 – 1.029

CTPA, Computed Tomography Pulmonary Angiography. PE, pulmonary embolism.

Association between Patient Gender, PE Symptoms, Wells Criteria, Wells score with PE

Variables tested for correlation with PE diagnosis include clinical signs of PE (shortness of breath, chest pain, and haemoptysis), Wells criteria (tachycardia, clinical sign and symptoms of DVT, recent surgery or immobilization, history of DVT/PE, and history of malignancy) and Wells score. However, only shortness of breath (p = 0.028) and increasing Wells score (p = 0.038, OR = 1.15, 95% CI: 1.01–1.31) showed statistically significant associations with PE diagnosis. These findings are summarized in table II.

D-dimer Testing

D-dimer testing was done in 240 patients (66.5%). Among the "PE unlikely" group, 79 (60.8%) were tested, 14 (17.7%) were positive for PE. In the "PE likely" group, 161 (69.7%) were tested despite guidelines not requiring it. Out of which 78 were PE positive (33.8%).

Adherence to Clinical Guidelines

The Wells Score was used in 78.5% of cases, but only 32.1% adhered strictly to the local guidelines, which recommend imaging only for "PE likely" or "PE unlikely" with positive D-dimer, as outlined in the Malaysian Clinical Practice Guidelines on Prevention and Treatment of Venous Thromboembolism4.

Statistical Association

Shortness of breath significantly correlated with PE diagnosis (p = 0.028). Logistic regression showed increasing Wells Score was significantly associated with PE (p = 0.038, OR = 1.15, 95% CI: 1.01–1.31). Findings are shown in table III.

DISCUSSION

Diagnostic yield is the metric used in assessing the appropriate of CTPA use. In many Western settings, yields

range between 6% and 15%. The value less than 10% is often cited as overutilization.[2,5-6] Such low yields are attributed to indiscriminate imaging, inconsistent use of clinical decision rules, and defensive medicine. In contrast, the diagnostic yield in this study was 29.6%, indicating that CTPA was appropriately utilized. This high yield is also observed in other regional studies. A study at a hospital in Kuantan, for example, reported a CTPA positivity rate of 26.5%, while other regional studies in Thailand and Singapore have also shown yields exceeding 20%.[7-8] These results suggest that, in contrast to many Western institutions, clinicians in this region are more selective when ordering CTPA, possibly due to differences in patient flow, access, or reliance on clinical judgment in resource-conscious environments.

Despite the high diagnostic yield, adherence to the guideline was suboptimal. Only 32.1% of patients followed the recommended pathway. This reliance on clinical judgment, though valid in experienced hands, introduces variability. The underuse of D-dimer in low-risk cases and overuse in high-risk cases reflects inconsistent application of the diagnostic algorithm. Nearly 40% of "PE unlikely" patients did not receive D-dimer testing, missing an opportunity to avoid imaging. Meanwhile, 70% of "PE likely" patients had unnecessary D-dimer testing. These practices may be influenced by habitual clinical behaviour, defensive medicine, or the conservative stance of the Malaysian VTE guideline regarding D-dimer use, which partly stems from historical concerns about assay sensitivity and standardisation.[4] However, D-dimer is highly sensitive for PE (sensitivity 96.2%, specificity 50%) [10] and is recommended by NICE guideline in patients with a low Wells score, with imaging reserved for those with positive results. The Pulmonary Embolism Rule-out Criteria (PERC) may also be applied in very low-risk patients to determine whether D-dimer testing is necessary.

The inconsistent application of the Wells Score and D-dimer pathway points to a gap between evidence-based recommendations and real-world clinical practice. Reliance on clinical judgement alone risks variability, inefficiency, and potential overtesting in less experienced settings. Although local cost data are unavailable, international studies have shown that inappropriate CTPA use imposes a significant financial burden. In Australia, the cost of a single CTPA is approximately AUD 530, with total costs per confirmed PE diagnosis rising up to AUD 21,800 when used in low-risk patients.[11] Conversely, Ong et al. reported a saving of AUD 61,710 after reducing 121 unnecessary CTPA scans over seven months through improved adherence to clinical prediction rules.[11]

Embedding validated decision rules into clinical workflows , such as integrating the Wells Score into electronic ordering systems or mandating documentation prior to CTPA referral could standardize decision-making, reduce unnecessary imaging, and improve resource stewardship. These interventions have been shown in other settings to increase guideline adherence and diagnostic yield without compromising patient safety.[6,9]

CONCLUSION

This study demonstrated a high diagnostic yield of CTPA for suspected pulmonary embolism, suggesting appropriate overall utilization. However, adherence to the local clinical guideline, particularly the use of Wells Score and D-dimer was suboptimal. We recommend bridging the gap between recommended practice and real-world decision-making by integrating the Wells score in electronic ordering system to further improve diagnostic efficiency, and support evidence-based care.

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The spectrum of developmental and epileptic encephalopathies and their genetic heterogeneity are much broader than previously thought

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Letter to the Editor

We read with interest the article by Triono et al., on a review using the PRISMA guidelines on the genetic causes of developmental and epileptic encephalopathy (DEE) and the phenotypes of these genetic disorders.[1] A total of 18 studies were included in the review, and the most frequently reported mutated genes were STXBP1 in Ohtahara syndrome, SLC1A2 in early myoclonic encephalopathy (EME), CDKL5 in West syndrome, SCN1A in Dravet syndrome, and KCNT1 in infantile epilepsy with migrating focal seizures (EIMFS) [1]. Each mutation was associated with different electroclinical features, including differences in age of onset, seizure type, EEG patterns, and developmental outcomes.[1] The overview is remarkable, but some points should be discussed.

The first point is that it is incomprehensible why patients with congenital mitochondrial disorders that manifest themselves in seizures and subsequently worsen due to epilepsy that is often difficult to treat were not included in the overview. In particular, patients with Leigh syndrome should have been included in the overview, as these patients are relatively common, the syndrome results from a broad spectrum of >100 mutated genes, progresses with the duration of the disease, often manifests itself through therapy-resistant seizures, and progresses with the number of seizures. Particularly, Alpers-Huttenlocher syndrome, POLG-associated mitochondrial syndromes, MERRF syndrome, and patients with MEGDEL syndrome should be included. It is also unclear why no patients with non-syndromic or syndromic microdeletion or microduplication disorders were included in the overview. This patient group includes, for example, 15q13.3 microdeletion syndrome or 3q29 microdeletion syndrome. It is also unclear why Lennox-Gastaux syndrome, myoclonic atonic epilepsy (Doose syndrome), Landau-Kleffner syndrome, epileptic encephalopathy with continuous spike-and-wave seizures during sleep, and fever-induced epilepsy syndrome (FIRES) are not mentioned.[2,3]

The second point concerns the discrepancy between the statement in the summary that the causes of DEE and the causes of variations are unknown, and the statement in the introduction that recent studies have shown that genetic causes have been identified in various epileptic encephalopathies and that various previously unknown genes have emerged.[1] The review itself has shown that the causes of DEE and the causes of variations are no longer unknown.

In summary, the review by Triono et al. is incomplete, as the spectrum of DEE is much broader than assumed. Expanding the review to include the many DEEs that were not considered could significantly increase reader interest and enhance the review's significance.

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