Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 79

Issue No: 6

November 2024

ISSN 0300-5283 PP 2121/01/2013 (031329) MITA(P) 124/1/91

MJM

Official Journal of the Malaysian Medical Association

Volume 79 Number 6 November 2024

EDITORIAL BOARD

PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 0300-5283

The Medical Journal of Malaysia is published six times a year.
MJM is published bimonthly ie. January, March, May, July, September and November.

Advertisement Rates:
Enquiries to be directed to the Secretariat.

Subscription Rates:
Price per copy is RM100.00 or RM360.00 per annum, for all subscribers.

Secretariat Address:
Malaysian Medical Association
4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
Website: www.mma.org.my

Printed by: Digital Perspective Sdn. Bhd.
42-1, Level 1, Plaza Sinar, Taman Sri Sinar, 51200 Kuala Lumpur. Tel: 03-6272 3767
Email: dpsbkl@gmail.com

The Medical Journal of Malaysia

MJM

INSTRUCTION TO AUTHORS

The *Medical Journal of Malaysia* ***(MJM)*** welcomes articles of interest on all aspects of medicine in the form of original papers, review articles, short communications, continuing medical education, case reports, commentaries and letter to Editor. Articles are accepted for publication on condition that they are contributed solely to *The Medical Journal of Malaysia*.

NOTE: MJM is published bimonthly ie. January, March, May, July, September and November.

REQUIREMENTS FOR ALL MANUSCRIPTS
Please ensure that your submission to MJM conforms to the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Neither the Editorial Board nor the Publishers accept responsibility for the views and statements of authors expressed in their contributions.

The Editorial Board further reserves the right to reject papers read before a society. To avoid delays in publication, authors are advised to adhere closely to the instructions given below.

MANUSCRIPTS
Manuscripts should be submitted in English (British English). Manuscripts should be submitted online through *MJM Editorial Manager*, http://www.editorialmanager.com/mjm.

Instructions for registration and submission are found on the website. Authors will be able to monitor the progress of their manuscript at all times via the *MJM Editorial Manager*. For authors and reviewers encountering problems with the system, an online Users' Guide and FAQs can be accessed via the "Help" option on the taskbar of the login screen.

MJM charges a one-time, non-refundable Article Processing Charge (APC) upon submission. Waiver of the APC applies only to members of the editorial board, and authors whose articles are invited by the editor. In addition, recipients of the MJM Reviewer Recognition Award from the previous year may enjoy a waiver of the APC for the next calendar year (e.g. recipients of MJM Reviewer Recognition Award 2022 will enjoy waiver of APC for articles submitted between January and December 2023).

MJM
Member: RM500
Non Member: RM800
Overseas: USD200

MJM Case Report
Member: RM400
Non Member: RM500

Preparing your manuscript

The MJM Article Processing Charge is a non-refundable administrative fee. Payment of the APC does not guarantee acceptance of the manuscript. Submitted articles will only be sent for reviews once the MJM APC has been successful completed.

All submissions must be accompanied by a completed **Copyright Assignment Form**, **Copyright Transfer Form and Conflict of Interest Form** duly signed by all authors. Forms can be download from MJM website at https://www.e-mjm.org/

Manuscript text should be submitted as **Microsoft Word** documents. Tables and flow-charts should be submitted as **Microsoft Word** documents. Images should be submitted as separate **JPEG files** (minimum resolution of 300 dpi).

PEER REVIEW PROCESS
All submissions must include at least two (2) names of individuals who are especially qualified to review the work. All manuscripts submitted will be reviewed by the Editor in-charge before they are send for peer review. Manuscripts that are submitted to MJM undergo a double-blinded peer review and are managed online. Proposed reviewers must not be involved in the work presented, nor affiliated with the same institution(s) as any of the authors or have any potential conflicts of interests in reviewing the manuscript. The selection of reviewers is the prerogative of the Editors of MJM.

ELIGIBILITY AS AN AUTHOR
MJM follows the recommendation of the International Committee of Medical Journal Editors (ICMJE) for eligibility to be consider as an author for submitted papers. The ICMJE recommends that authorship be based on the following four (4) criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TYPES OF PAPERS
Original Articles:
Original Articles are reports on findings from original unpublished research. Preference for publications will be given to high quality original research that make significant contribution to medicine. Original articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. The main text of the articles should not exceed 4000 words, tables/illustrations/figures/images up to five (5) and references up to 40. Manuscript describing original research should conform to the IMRAD format, more details are given below.

Original articles of cross-sectional and cohort design should follow the corresponding STROBE check-lists; clinical trials should follow the CONSORT check-list.

Review Articles:
Review Articles are solicited articles or systematic reviews. ***MJM*** solicits review articles from Malaysian experts to provide a clear, up-to-date account of a topic of interest to medical practice in Malaysia or on topics related to their area of expertise. Unsolicited reviews will also be considered, however, authors are encouraged to submit systematic reviews rather than narrative reviews. Review articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. Systematic Review are papers that presents exhaustive, critical assessments of the published literature on relevant topics in medicine. Systematic reviews should be prepared in strict compliance with MOOSE or PRISMA guidelines, or other relevant guidelines for systematic reviews.

Short Communications:
Shorts communication are short research articles of important preliminary observations, findings that extends previously published research, data that does not warrant publication as a full paper, small-scale clinical studies, and clinical audits. Short communications should not exceed 1,500 words and shall consist of a Summary and the Main Text. The summary should be limited to 100 words and provided immediately after the title page. The number of tables/illustrations/figures/images should be limited to three (3) and the number of references to ten (10).

Continuing Medical Education (CME) Articles:
A CME article is a critical analysis of a topic of current medical interest. The article should include the clinical question or issue and its importance for general medical practice, specialty practice, or public health. It shall consist of a Summary and the Main Text. The summary should be limited to 500 words and provided immediately after the title page Upon acceptance of selected articles, the authors will be requested to provide five multiple-choice questions, each with five true/false responses, based on the article. For guideline, please refer to: Sivalingam N, Rampal L. Writing Articles on Continuing Medical Education for Medical Journals. Med J Malaysia. 2021 Mar;76(2):119-124.

Case Reports:
Papers on case reports (one to five cases) must follow these rules: Case reports should not exceed 2,000 words; with a maximum of two (2) tables; three (3) photographs; and up to ten (10) references. It shall consist of a Summary and the Main Text. The summary should be limited to 250 words and provided immediately after the title page. Having a unique lesson in the diagnosis, pathology or management of the case is more valuable than mere finding of a rare entity. Being able to report the outcome and length of survival of a rare problem is more valuable than merely describing what treatment was rendered at the time of diagnosis. There should be no more than seven (7) authors.

Please note that all Case Reports will be published in the new MJM Case Reports Journal (www.mjmcasereports.org).

Commentaries:
Commentaries will usually be invited articles that comment on articles published in the same issue of the ***MJM***. However, unsolicited commentaries on issues relevant to medicine in Malaysia are welcomed. They should not exceed 2,000 words. They maybe unstructured but should be concise. When presenting a point of view, it should be supported with the relevant references where necessary.

Letters to Editor:
Letters to Editors are responses to items published in ***MJM*** or to communicate a very important message that is time sensitive and cannot wait for the full process of peer review. Letters that include statements of statistics, facts, research, or theories should include only up to three (3) references. Letters that are personal attacks on an author will not be considered for publication. Such correspondence must not exceed 1,500 words.

Editorials:
These are articles written by the editor or editorial team concerning the ***MJM*** or about issues relevant to the journal.

STRUCTURE OF PAPERS
Title Page:
The title page should state the brief title of the paper, full name(s) of the author(s) (with the surname or last name bolded), degrees (limited to one degree or diploma), affiliation(s), and corresponding author's address. All the authors' affiliations shall be provided after the authors' names. Indicate the affiliations with a superscript number at the end of the author's degrees and at the start of the name of the affiliation. If the author is affiliated to more than one (1) institution, a comma should be used to separate the number for the said affiliation.

Do provide preferred abbreviated author names for indexing purpose, e.g. L Rampal (for Lekhraj Rampal), BS Liew (for Liew Boon Seng), B Abdullah (for Baharudin Abdullah), Hoe VC (for Victor Hoe Chee Wai).
Please indicate the corresponding author and provide the affiliation, full postal address and email.

Articles describing Original Research should consist of the following sections (IMRAD format): Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgment and References. Each section should begin on a fresh page.
Scientific names, foreign words and Greek symbols should be in italic.

Abstract and Key Words:
A structured abstract is required for Original and Review Articles. It should be limited to 500 words and provided immediately after the title page. Below the abstract provide and identify three (3) to 10 key words or short phrases that will assist indexers in cross-indexing your article. Use terms from the medical subject headings (MeSH) list from Index Medicus for the key words where possible. Key words are not required for Short Communications, CME articles, Case Reports, Commentaries and Letter to Editors.

Introduction:
Clearly state the purpose of the article. Summarise the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Materials and Methods:
Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly, identify the methods, apparatus (manufacturer's name and address in parenthesis), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well-known; describe new or substantially modified methods, give reasons for using them and evaluate their limitations.

Identify precisely all drugs and chemicals used, including generic name(s), dosage(s) and route(s) of administration. Do not use patients' names, initials or hospital numbers. Include numbers of observation and the statistical significance of the findings when appropriate.

When appropriate, particularly in the case of clinical trials, state clearly that the experimental design has received the approval of the relevant ethical committee.

Results:
Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations, or both: emphasise or summarise only important observations in the text.

Discussion:
Emphasise the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies.

Conclusion:
Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgements:
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

Referencing guide:
The Medical Journal of Malaysia, follows the Vancouver numbered referencing style. Citations to someone else's work in the text, should be indicated by the use of a number. In citing more than one article in the same sentence, you will need to include the citation number for each article. A hyphen should be used to link numbers which are inclusive, and a comma used where numbers are not consecutive. The following is an example where works 1.3,4,5.have been cited in the same place in the text.

Several effective drugs are available at fairly low cost for treating patients with hypertension and reducing the risk of its sequelae.[1,3-5]

The list of all of the references that are cited in the article should be presented in a list labelled as 'References'. This reference list appears at the end of the paper. Authors are responsible for the accuracy of cited references and these should be verified by the author(s) against the original documents before the manuscript is submitted. It is important that the author should never place in the list of references a document that he or she has not seen. The Journals names should be abbreviated according to the style used in the Index Medicus. All authors when six or less should be listed; when seven or more list only the first six and add et al.

If you are citingthe author's name in your text, you must insert the citation number as well. Jewell BL (8) underlined that as focus in the SARS-CoV-2 pandemic shifts to the emergence of new variants of concern (VOC), characterising the differences between new variants and non-VOC lineages will become increasingly important for surveillance and maintaining the effectiveness of both public health and vaccination programme. If you are citing more than one author's name in your text and you want to cite author names in your text, use 'et al.' after the first author. Example: Rampal et al. (9) highlighted that the. disregard of the manuscript guidelines and instruction to authors of the journal you submit, is one of the common reasons for 'Rejection' of the article.

Example references Journals:
Standard Journal Article
Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

Chapter in Book
McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.

Corporate Author
World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260–64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

Online articles
Webpage: Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

Other Articles:
Newspaper Article
Panirchellvum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).

Magazine Article
Rampal L.World No Tobacco Day 2021 -Tobacco Control in Malaysia. Berita MMA. 2021; May: 21-22.

Tables:
All tables and figures should have a concise title and should not occupy more than one printed page. The title should concisely and clearly explain the content of the table or figure. They should be numbered consecutively with Roman numerals (e.g Table I) and figures with Arabic numerals (e.g. Figure 1), and placed after the sections of the manuscript which they reflect, particularly the results which they describe on separate pages. Cite tables in the text in consecutive order. Indicate table footnotes with lower-case letters in superscript font. Place the information for the footnote beneath the body of the table. If a table will be submitted as a separate document, the filename should contain the surname of the first author and match its label in the manuscript (e.g., SMITH Table I).Vertical lines should not be used when constructing the tables. All tables and figures should also be sent in electronic format on submission of the manuscript as supplementary files through the journal management platform. Clinical Photographs should conceal the subject's identity. Tables and flow-charts should be submitted as Microsoft Word documents. Images should be submitted as separate JPEG files (minimum resolution of 300 dpi).

Photographs of Patients:
Proof of permission and/or consent from the patient or legal guardian must be submitted with the manuscript. A statement on this must be included as a footnote to the relevant photograph.

Colour reproduction:
Illustrations and diagrams are normally reproduced in black and white only. Colour reproductions can be included if so required and upon request by the authors. However, a nominal charge must be paid by the authors for this additional service; the charges to be determined as and when on a per article basis.

Abbreviations:
Use only standard abbreviations. The full-term for which an abbreviation stands should precede its first use in the abstract, article text, tables, and figures, unless it is a standard unit of measurement. Abbreviations shall not be used in the Title. Abbreviations should be kept to a minimum.

Formatting of text:
Numbers one to ten in the text are written out in words unless they are used as a unit of measurement, except in tables and figures. Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph. Do not use the automated formatting of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Submit the Manuscript in plain text only, removed all 'field codes' before submission. Do not include line numbers. Include only page number.

BEST PAPER AWARD
All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

CONTENTS Page

Original Articles

CONTENTS Page

ORIGINAL ARTICLE

Drug-resistant tuberculosis in Malaysia: Prevalence, characteristics, and treatment outcomes

Mohd Fahmin Kamarul Zaman, MPH[1], Mohd Yusof Sidek, MCommMed (Occupational Health)[1], Nik Rosmawati Nik Husain, PhD[1], Zamzurina Abu Bakar, Fellowship of Respiratory Medicine (Malaysia)[2]

[1]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Institute of Respiratory Medicine, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Drug-resistant tuberculosis (DR-TB) poses a serious global health threat, leading to high morbidity and mortality rates. Malaysia has witnessed an increase in DR-TB cases, necessitating research into trends and characteristics. This study aims to determine the prevalence and describe the characteristics and treatment outcomes of DR-TB cases in Malaysia from 2016 to 2020.

Materials and Methods: A retrospective record review was carried out, utilising secondary data obtained from the TB registry of Selangor and Wilayah Persekutuan Kuala Lumpur. All registered DR-TB cases between 2016 and 2020 that met the study criteria were analysed descriptively using SPSS software version 27.

Results: Of 443 cases of registered DR-TB over 5 years, 430 cases fulfilled the study criteria. The prevalence of DR-TB increased from 0.27 to 1.79 per 100,000 population between 2016 and 2020. The average age was 40.96 years, majority were males (70.7%), Malaysian (79.3%), with Malays comprising 50.2%. Most patients had up to secondary school education (51.9%), married (57.0%), employed (53.3%) and 34.9% were smokers. For clinical characteristics, 23.5% had diabetes, and 10.9% were HIV-positive. Retreatment cases accounted for half the total, and 83.9% had positive smear results. Minimal chest X-ray lesions were observed in 54.4% of cases. The majority (66.7%) received supervised treatment from healthcare providers after being diagnosed with DR-TB, and 37.4% had more than one anti-TB resistance. Favourable treatment outcomes were observed in 56.7% of cases, while 42.1% had unfavourable outcomes, mainly due to loss to follow-up (49.7%), death (42.6%) and treatment failure (7.7%).

Conclusion: The rising cases of DR-TB call for comprehensive public health interventions and stakeholder commitment to reduce its occurrence and transmission. These findings provide valuable guidance for policymakers in strengthening DR-TB control and prevention strategies.

KEYWORDS:
Tuberculosis, drug-resistant, prevalence, outcomes, Malaysia

INTRODUCTION

Malaysia is an intermediate tuberculosis (TB) burden country, with a TB notification rate ranging from 10 to 99 cases per 100,000 population.[1] The Ministry of Health (MOH) Malaysia developed the National Strategic Plan for Tuberculosis Control (2016–2020) to support the goal of eliminating TB by 2035, aligned with the WHO End TB Strategy. However, the rise of drug-resistant tuberculosis (DR-TB) has become a significant challenge despite the disease being treatable and preventable. According to WHO Consolidated Guidelines on TB, DR-TB is defined as TB disease caused by Mycobacterium tuberculosis (MTB) strains that are resistant to standard TB medications.[2] Mutations in MTB led to the development of resistance, causing specific treatments or medications to lose their effectiveness against the pathogen.[3] The current categorisation of DR-TB introduced by WHO in 2021 includes isoniazid-resistant tuberculosis (HR-TB), rifampicin-resistant tuberculosis (RR-TB), multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), along with the addition of pre-extensively drug-resistant tuberculosis (pre-XDR TB).[4–5] Compared to the previous classification, where all categories are not mutually exclusive, the current system now includes HR-TB and introduces the new category of pre-XDR TB.[6,7] Globally, almost half a million people developed RR-TB, of which 78% progressed to MDR-TB, with countries like India, China and the Russian Federation bearing significant burdens.[8,9] The Global Burden of Disease study from 2017 indicates that the incidence of MDR-TB showed a significant upward trend worldwide between 1990 and 1999, with the overall age-standardised incidence rate (ASIR) increasing at an average annual rate of 17.63%.[10] However, research and published data on MDR-TB in Malaysia are scarce. The Malaysian Ministry of Health reported 192 cases of DR-TB in 2019.[11]

Treating patients with DR-TB is more complex, costly and time-consuming than patients with susceptible TB strains. Additionally, DR-TB commonly has toxicity and adverse effects from the anti-TB regimen instituted.[12] Inappropriate treatment regimes, poor quality of drugs, concomitant medical diseases and non-adherence to medications are significant determinants of drug resistance, leading to high mortality rates and substantial financial consequences.

This article was accepted: 08 September 2024
Corresponding Author: Mohd Yusof Sidek
Email: dryusofs@usm.my

Therefore, Malaysia has outlined several strategic interventions to combat DR-TB effectively. Among these, Strategy 4 focusses on strengthening the programmatic management of DR-TB. This strategy aims to enhance early detection, improve patient management, update national guidelines and ensure the availability of resources and training. Key activities under Strategy 4 include the implementation of rapid diagnostic tools, mandatory notifications and comprehensive guidelines for patient management and surveillance.[1] Despite these proactive strategies, there remains a significant gap in assessing the actual burden of the disease. A lack of understanding of the characteristics and insights into the DR-TB burden could exacerbate the DR-TB crisis, leading to increased mortality and economic strain on both the healthcare system and affected individuals. Therefore, this study aims to assess the burden and describe the characteristics of DR-TB patients in Malaysia for 5 years. The findings would contribute to formulating targeted interventions and refining strategies to combat the challenges associated with DR-TB.

MATERIALS AND METHODS

Study Setting and Participants Selection

A cross-sectional study was conducted from December 2022 to May 2023 using secondary data from the Ministry of Health Malaysia's (MOH) National Tuberculosis Registry (NTBR). The study included DR-TB cases registered in NTBR and residing in Selangor and Wilayah Persekutuan Kuala Lumpur (WPKL), Malaysia. To ensure the accuracy of data analysis for DR-TB treatment outcome, cases with missing or incomplete data exceeding 30%, change of diagnosis, or transfer out of the study area were excluded. According to the notification and reporting of DR-TB cases by the MOH, DR-TB is classified based on drug sensitivity testing (DST) in clinical isolates confirmed as MTB. There are five types: isoniazid-resistant tuberculosis (HR-TB) entails resistance to isoniazid alone, with confirmed rifampicin susceptibility in vitro; MDR-TB manifests as resistance to at least both isoniazid and rifampicin; Pre-XDR-TB encompasses MDR/RR-TB and resistance to any fluoroquinolone; extensively drug-resistant tuberculosis (XDR-TB) includes MDR/RR-TB and resistance to any fluoroquinolone plus at least one additional Group A drug; rifampicin-resistant tuberculosis (RR-TB) indicates rifampicin resistance using phenotypic or genotypic methods, potentially with other anti-TB drug resistance, encompassing monoresistant, polyresistant, MDR or XDR. In previous years, the definition of DR-TB included categories such as monodrug and polydrug resistance, which were not mutually exclusive and primarily focused on resistance to the first-line drugs isoniazid and rifampicin, classifying cases as MDR-TB. However, in this current study, we adopted the updated classification from the WHO Global TB Report 2021, which streamlines DR-TB into five distinct categories as previously mentioned, including the updated definition of XDR-TB and the introduction of pre-XDR-TB.

Sample size determination and sampling method

The sample size was calculated using a single proportion formula with a web sample size calculator (https://wnariffin.github), considering an 80% power of the study and 5% type I error rate. The proportion of MDR-TB in Sabah, Malaysia, was used as a reference (0.003), along with a precision of 0.0015. Additionally, 10% of the potential for missing or incomplete data was considered. Since the population of Selangor is approximately 7 million, and WPKL is around 2 million, the estimated sample size was deemed acceptable. Meanwhile, the two independent proportions formula was used to calculate the sample size of DR-TB cases to be included when assessing for characteristics and treatment outcomes. A total of 444 cases were needed. Therefore, no sampling was conducted due to the limited number of cases, and all 430 DR-TB cases registered in the NTBR of Selangor and WPKL from January 2016 to December 2020, that met the study criteria were included in the analysis.

Data collection

Data were collected from two primary sources: the NTBR and the line listing of DR-TB cases. NTBR is a centralised electronic TB information system used by healthcare professionals at various levels of the healthcare system in Malaysia. It contains comprehensive details on TB cases and contacts, including sociodemographic, clinical, laboratory, treatment and follow-up information. The line listing of DR-TB cases is a data comparison to the registered cases in NTBR and includes data from the TB Information System (TBIS) 10G and DRTBIS 50A-1. TBIS 10G provides information on TB cases that have failed first-line treatment and contributing factors, while DRTBIS 50A-1 is used for the registration of all DR-TB cases, regardless of whether treatment has been initiated.

Data extraction was guided by a proforma checklist, focusing on sociodemographic characteristics, social history (smoking history), clinical characteristics and treatment outcomes. Sociodemographic features included age, sex, nationality, ethnicity, level of education, marital status and employment status. Clinical aspects covered comorbidities (diabetes mellitus and HIV), the treatment category, either new or retreatment, smear positivity, chest x-ray results, directly observed treatments (DOTS) supervision and the category of DR-TB. Treatment outcomes are either cured, completed, failed, death, loss to follow-up, not evaluated and treatment success. Population density data for Selangor and Wilayah Persekutuan Kuala Lumpur were obtained from the Department of Statistics Malaysia's (DOSM) website to calculate the prevalence of DR-TB.

Statistical Analysis

IBM SPSS version 27 was used for data entry and analysis. The data was cleaned once it was entered. A preliminary data description was performed to discover any missing values. The data set was reviewed for inaccuracies and corrected as necessary. To calculate the prevalence of DR-TB, the below formula was used, and the results are expressed over 100,000 population.

$$\text{Prevalence} = \frac{\text{Total number of DR-TB cases in Selangor and WPKL in a given year}}{\text{Total population in Selangor and WPKL in a given year}} \times 100{,}000$$

A descriptive analysis was conducted on the patients' characteristics and treatment outcomes. Categorical data is expressed as frequency and percentage, while normally distributed numerical data is expressed as mean and standard deviation (SD). Treatment outcomes were categorised into unfavourable or favourable outcomes. Favourable treatment outcomes include cases categorised as cured and treatment completed. Unfavourable outcomes encompass cases designated as treatment failure, death, and loss to follow-up.[6]

RESULTS

Prevalence rate of DR-TB cases

During a 5-year period from 2016 to 2020, 443 cases of DR-TB were notified and registered for the first time in the NTBR database for Selangor and WPKL. After excluding 13 cases due to missing data, diagnostic changes or transfer out of the study area, 430 cases met the study criteria. The yearly number and calculated prevalence rate of DR-TB cases in Selangor and WPKL from 2016 to 2020 are shown in Table I. Over 5 years, there was a gradual increase in the number of DR-TB patients. The prevalence rate of DR-TB shows a steady rise, climbing from 0.27 in 2016 to 1.79 in 2020.

DR-TB treatment outcomes

Within this group, there were 244 cases with favourable treatment outcomes, 181 with unfavourable outcomes, and five with ongoing treatment, constituting 56.7%, 42.1% and 1.2% of the total, respectively. Figure 1 depicts that among the 181 cases of unfavourable treatment outcomes in DR-TB patients, the majority were due to loss to follow-up (49.7%), followed by death (42.6%), and a smaller proportion resulted from treatment failure (7.7%).

Characteristics of DR-TB cases

For sociodemographic characteristics, the ages of individuals diagnosed with DR-TB ranged from 26 to 56 years old, with a mean of 40.96 (SD = 15.04) years. Meanwhile, the bulk of the cases were males, with 304 cases (70.7%), while Malaysians predominated with 341 cases (79.3%), with 216 cases (50.2%) being Malays. Furthermore, the majority of the patients had education up to secondary school (51.9%), married (57.0%) and employed (53.3%), as presented in Table II. Smokers constitute one-third of total DR-TB cases (34.9%).

Meanwhile, for clinical characteristics, among patients with DR-TB, 23.5% had diabetes, and 10.9% were HIV-positive. The treatment category almost equally represented new cases and retreatment cases. These findings also imply that the majority of DR-TB patients (83.9%) showed positive smear results, while 15.6% were negative and a small percentage (0.5%) did not undergo smear testing, potentially influencing their treatment outcomes. Regarding chest x-ray results, most DR-TB patients (54.4%) had minimal lesions, 41.2% showed moderate to far advanced lesions and 4.4% had no lesions. Among DR-TB cases, the majority were MDR/Pre-XDR/XDR-TB, followed by HR-TB and RR-TB. DOT supervision from healthcare workers was received in two-thirds of the cases (66.7%) after being diagnosed as DR-TB. Family members also played a significant role in providing supervision but to a lesser extent. A small number of patients received no monitoring or supervision other than the two categories mentioned. Further details on the clinical characteristics of DR-TB cases are summarised in Table III.

DISCUSSION

Individuals from marginalised communities are disproportionately affected by DR-TB.[13] They often face challenges such as adverse drug reactions, high treatment costs, social stigma and discrimination. These factors, along with clinical considerations, significantly impact treatment outcomes. Addressing this issue is crucial, given the global concern about the low rate of favourable outcomes in DR-TB cases. Therefore, this study was designed to determine the prevalence rate and to describe the sociodemographic and clinical characteristics of DR-TB cases, providing valuable insights for our national TB policy-making efforts.

Prevalence of DR-TB

The current study, based on data from the NTBR, revealed an increase in the prevalence of DR-TB cases in Selangor and WPKL, ranging from 0.27 to 1.79 per 100,000 population. Selangor, with a population of 6.9 million, is the state with the greatest Malaysian population composition, at 21.6% in 2020, and has a population density of 880 people per square kilometre. In comparison, WPKL, with a population of 1.9 million, has the highest population density in Malaysia, with 8,045 people per square kilometre.[14] The low number of cases observed during the initial 2-year period of the study could have led to an underestimated prevalence rate in these two states, attributed to the low number of DR-TB cases being notified and registered in the NTBR database during that time. International studies reported the DR-TB prevalence within the range of 3–5%. For instance, Amin et al.[15] reported a prevalence of 3.8% in Ethiopia, while Al Ammari et al.[16] and Sambas et al.[17] reported rates of 4.4% and 5.0%, respectively, both from Saudi Arabia. Additionally, from 2010 to 2012, the prevalence of DR-TB at one hospital in Bangkok, Thailand, was found to be 2.6%.[18] Locally, Goroh et al.[19] found that MDR-TB prevalence was 0.3% of TB cases. The study used a retrospective record review of 33,193 TB cases from the NTBR database reported in Sabah, Malaysia, between 2012 and 2018.

The observed rise in reported DR-TB cases after 2018 may reflect changes in reporting criteria rather than a true increase in incidence. Reporting is based on administrative instructions from the Disease Control Division rather than being mandated by law, so the reported numbers may not accurately represent the actual number of cases. Initially, the 2013 instructions required reporting only MDR-TB and XDR-TB. These criteria were expanded in 2018 to include more detailed reporting for MDR and XDR-TB and were further refined in 2020 to include HR-TB.[11] Improved notifications and documentation practices via state line listing and regular updates between district health offices and treatment centres ensure accurate surveillance. The national TB surveillance system, reinforced by the NTBR electronic TB information system introduced in 2012, supports this enhanced monitoring. Additionally, better programmatic management of DR-TB, as outlined in the National Strategic Plan's fourth

Table I: Prevalence of DR-TB cases in Selangor and WPKL from 2016 to 2020

Year	No. of population	No. of DR-TB cases	Prevalence of DR-TB* (95% CI)
2016	8,060,000	22	0.27 (0.19, 0.45)
2017	8,170,000	44	0.54 (0.39, 0.74)
2018	8,270,000	101	1.22 (0.99, 1.49)
2019	8,290,000	115	1.39 (1.18, 1.72)
2020	8,290,000	148	1.79 (1.55, 2.14)

*Prevalence over 100,000 population

Table II: Sociodemographic characteristics of DR-TB cases in Selangor and WPKL from 2016 to 2020 (n = 430)

Variables	Mean (SD)	Frequency (%)
Age* (years)	40.96 (15.04)	
Sex		
Female		126 (29.3)
Male		304 (70.7)
Citizenship		
Malaysian		341 (79.3)
Non-Malaysiana		89 (20.7)
Races		
Malay		216 (50.2)
Chinese		61 (14.2)
Indian		51 (11.9)
Others		102 (23.7)
Level of education		
No formal education		93 (21.6)
Primary		35 (8.1)
Secondary		223 (51.9)
Tertiary		79 (18.4)
Marital status		
Single		157 (36.5)
Married		245 (57.0)
Divorcee		28 (6.5)
Employment status		
Unemployed		201 (46.7)
Employed		229 (53.3)
Smoking status		
No		280 (65.1)
Yes		150 (34.9)

*Mean (SD)
[a]Indigenous peoples, Bumiputera Sabah and Sarawak, Non-Malaysian

strategy, has further contributed to improved detection and reporting of cases.

The rising trend of DR-TB in Malaysia is partly due to advancements in laboratory testing. GeneXpert testing, introduced in 2009, has revolutionised TB diagnostics with its Xpert MTB/RIF assay, which provides results in under 2 hours with high sensitivity (91% for culture-positive cases and 95.1% for rifampicin resistance).[20] Although GeneXpert testing has improved DR-TB detection, expanding its coverage is essential, as a significant portion of cases were not tested by culture, and culture positivity was low (26% among pulmonary cases).[19] Furthermore, in high HIV and TB prevalence settings, this testing has significantly enhanced the detection of active pulmonary TB, particularly among HIV-infected high-risk individuals.[21]

Treatment outcomes of DR-TB cases

This study found that 56.7% of DR-TB cases ended up with favourable treatment outcomes. Meanwhile, of the 181 cases of unfavourable treatment outcomes among DR-TB patients, the majority was attributed to loss to follow-up (49.7%), followed by death (42.6%), with a smaller proportion resulting from treatment failure (7.7%). In another study conducted in Vietnam by Wrohan et al.[22], among the 211 cases that experienced unfavourable treatment outcomes, loss to follow-up was also the most prevalent at 50.7%, followed by treatment failure at 25.6% and death at 23.7%. The observation that loss to follow-up has the highest percentage among unfavourable treatment outcomes in this study raises several critical considerations. Loss to follow-up might reflect challenges related to treatment adherence.[23]

Factors such as socioeconomic status, access to healthcare, patient education and support systems could contribute to individuals discontinuing their treatment prematurely.[7]

Table III: Clinical characteristics of DR-TB cases in Selangor and WPKL from 2016 to 2020 (n = 430)

Variables	n (%)
Diabetes mellitus	
No	329 (76.5)
Yes	101 (23.5)
HIV status	
Negative	383 (89.1)
Positive	47 (10.9)
Treatment category	
New cases	217 (50.5)
Retreatment cases	213 (49.5)
Smear positivity	
Negative	67 (15.6)
Positive	361 (83.9)
Not done	2 (0.5)
Chest x-ray	
No lesion	19 (4.4)
Minimal	234 (54.4)
Moderate/far advanced	177 (41.2)
DOT supervision	
Healthcare workers[a]	287 (66.7)
Family members	124 (28.8)
No supervision/others[b]	19 (4.5)
Category of DR-TB	
HR-TB	148 (34.4)
RR-TB	121 (28.2)
MDR/Pre-XDR/ XDR-TB	161 (37.4)

[a]including virtual DOT
[b]DOT by other than healthcare workers and family members
DOT = Directly observed treatmen

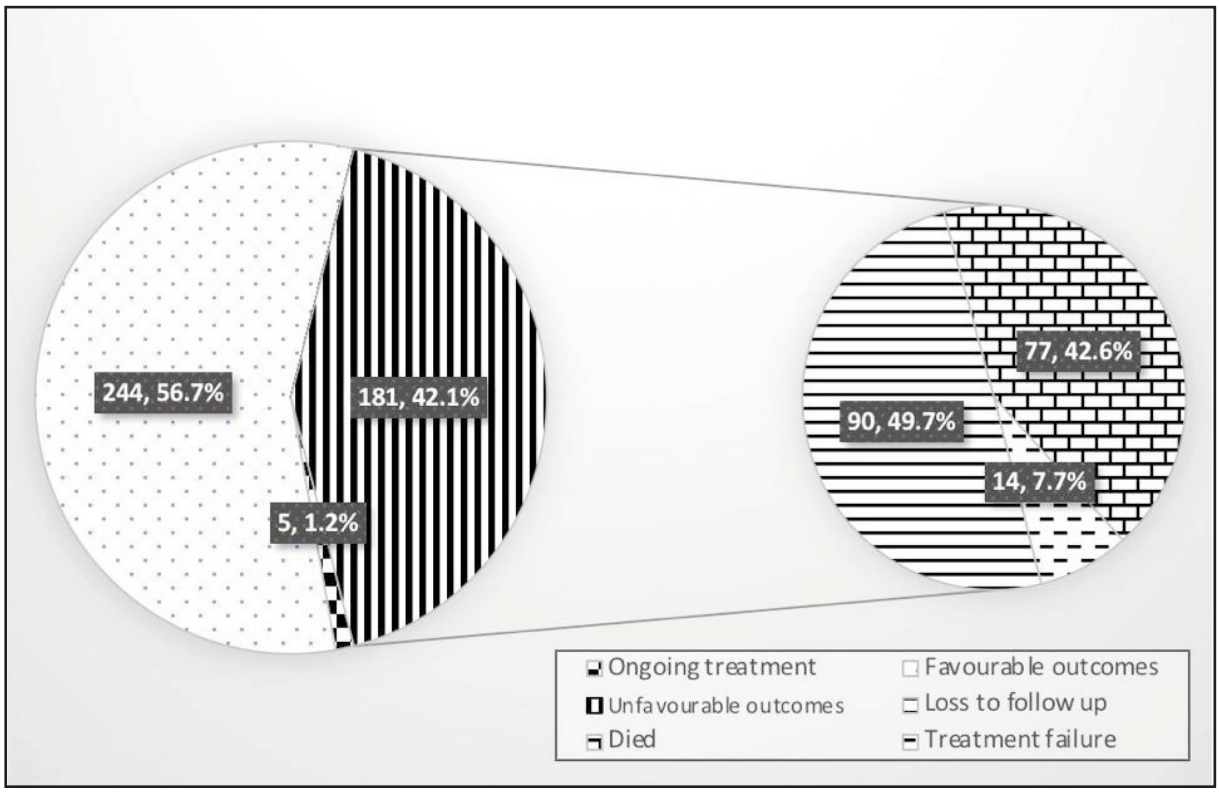

Fig. 1: Categories of treatment outcomes among DR-TB cases in Selangor and WPKL from 2016 to 2020

Suboptimal treatment not only jeopardises patient outcomes but also heightens the risk of disease transmission and the emergence of further drug resistance.[24] The stigma associated with TB and its treatment, along with societal attitudes towards the disease, could deter patients from continuing treatment.[25] DR-TB is more challenging to treat than drug-sensitive TB due to the longer and more expensive therapy required, along with potentially adverse side effects.[7] Therefore, strategies such as decentralising treatment services, providing financial support for transportation or treatment costs and establishing support groups should be considered.

Sociodemographic characteristics of DR-TB cases

This study found that DR-TB cases in Malaysia primarily affected adults aged 26 to 56 years, with a mean (SD) of 40.96 (15.04) years, potentially due to workplace transmission, impacting productivity and causing financial strain. Males were predominantly affected, consistent with earlier studies in Saudi Arabia,[16] Vietnam,[22] and China.[26] Males are considered at higher risk compared to females, probably due to their vulnerability and risk in terms of underlying comorbidities such as HIV infection, diabetes mellitus and chronic obstructive pulmonary disease (COPD), which are predominant in males; behavioural risk factors like smoking, illicit drug and alcohol abuse;[27,28] socio-cultural factors, for example occupational-related factors in certain male-predominant professions such as mining and construction;[15,29] and also health-seeking behaviour patterns as most male patients delay seeking treatment, resulting in delayed diagnosis and treatment initiation.[30] Malaysians comprised the majority, while Burmese and Indonesians predominate for non-citizens as a result of the influx of foreign workers in various industries.[31] Illegal or unpermitted foreign employees without proper health screening and the presence of refugees and asylum seekers complicate the situation. Regarding education, most of the cases (51.9%) had received education up to the secondary school, and 21.6% had no formal education, a finding similar to that reported by Liew et al.[32] Despite Malaysia's high literacy rate of 95.10% in 2017, the low post-secondary education enrolment (16-17%) raises concerns about educational access and attainment.[33] Health literacy impacts treatment adherence, disease awareness, health-seeking behaviour and socio-economic status.

Clinical Characteristics of DR-TB Cases

This study identified 23.5% of DR-TB patients as diabetics, and 10.9% were HIV-positive. Comparing this finding with another local study by Elmi et al.,34 the results were 26.7% and 5.7%, respectively. Another study in Saudi Arabia involving 2098 patients from the MDR-TB and RR-TB categories revealed an even lower percentage of DR-TB with diabetes mellitus and HIV-positive individuals (12.7% and 2.1%, respectively).[16] The variations could be due to differences in study populations, locations and changes in the HIV epidemic over time. The comorbidities can significantly impact the treatment outcomes of DR-TB in terms of a weakened immune system, leading to more severe disease, an increased risk of treatment failure, and higher mortality.[7] Managing concurrent DR-TB, HIV or diabetes is challenging due to potential drug interactions and adherence complexities, which require vigilant monitoring. Diabetes increased the likelihood of contracting TB by two- to three-fold when compared to non-diabetic controls. In addition, weakened immunity in individuals with diabetes may lead to the emergence of active TB from latent infection.[28] Therefore, early detection through HIV testing in new TB patients and TB screening in newly diagnosed HIV patients, as recommended by the National TB Control Programme, may improve treatment outcomes. The study also highlighted the importance of smear status in diagnosing DR-TB, with 83.9% of cases being smear-positive. Positive AFB smears, often indicating high mycobacterial loads, were associated with severe disease and unfavourable outcomes.[18] Smear positivity was identified as an independent risk factor for MDR-TB among previously treated patients, as reported by Law et al.[35] Despite aligning with MOH policy, the accuracy of DST for some anti-TB medications remains imperfect.[1] In fact, almost 20% of cases with smear-negative TB and no sputum were diagnosed as DR-TB in this study, underlining the challenges in diagnosing TB, possibly due to immunosuppression, early illness, or poor specimen quality.[36]

Regarding CXR findings, while 54.4% of cases had minimal lesions, a normal CXR can still be observed in approximately 4-5% of patients. Trained personnel interpreting CXRs significantly improved TB detection by 1.23-fold (95% CI: 1.02,1.48).[37] While the severity of CXR abnormalities may indicate disease progression and potential drug resistance, it is not the sole determinant; individuals' factors such as immune status and comorbidities also contribute.38 Meanwhile, for the type of drug resistance, WHO monitors and reports two main categories, which are MDR and RR-TB. In this study, MDR-TB predominates the DR-TB category with 156 cases (36.3%), followed by HR-TB (n = 148, 34.4%), and RR-TB (n = 121, 28.2%). The analysis also showed four cases of pre-XDR-TB and one case of XDR-TB. Elmi et al.[34] also highlighted that rifampicin had the highest degree of resistance, followed by isoniazid. The widespread use of rifampicin since its introduction in 1971, especially in the context of isoniazid-resistant organisms, has contributed to this rise in resistance.[39] As a result, the growing number of patients resistant to both isoniazid and rifampicin. Similar trends have been observed in other countries like Pakistan and Vietnam, where MDR/RR-TB accounts cases are prevalent.[22] Last but not the least, DOT is a critical element of TB treatment, where anti-TB medicine consumption is directly monitored by healthcare workers, trained family members or, in specific locations, trained community volunteers or a non-governmental organisation (NGO). It ensures patients take prescribed medications correctly, enhancing compliance. DOT was reportedly practised in Malaysia at 97% (93% to 100%).40 In our study, the majority of the cases (66.7%) were supervised by healthcare workers, including virtual DOT, followed by family members (28.8%) and others (1.4%). Sadly, 3.0% of cases had no DOT supervision from any of the personnel mentioned above or organisations. Lack of supervision led to unfavourable outcomes, emphasising the importance of consistent DOT throughout the treatment.

Limitations and recommendations for future studies

Despite the encouraging findings, a few limitations were encountered during this study. The assumed coverage of the

NTBR database would ideally be 100% of all TB cases within the studied region. However, given the limitations and challenges of data collection, entry errors, especially by a new or untrained user, and potential inconsistencies, achieving true 100% coverage and accuracy might not be guaranteed. As mentioned above, some necessary variables that can contribute extra knowledge about DR-TB are not available in NTBR. In addition, the number of cases couldn't reach the calculated sample size due to the small number of cases in the early 2 years of the study period. Therefore, all DR-TB cases with unfavourable treatment outcomes were considered. Proper documentation and improvement in DR-TB notification only started in 2018 through a clear written circular from MOH, with dedicated staff taking care of data at the state level in the TB Unit.

To improve DR-TB control across Malaysia, it is recommended to enhance the surveillance by strengthening our laboratory capacity and integrating advanced diagnostic tools such as GeneXpert for early detection. Additionally, focused research should be conducted to identify socioeconomic, environmental, and healthcare-related factors contributing to the rise in DR-TB cases. Capacity-building programs should also be implemented to improve healthcare professionals' ability to diagnose and manage DR-TB effectively.

CONCLUSION

The study highlights a concerning rise in Drug-resistant tuberculosis (DR-TB) prevalence in Malaysia from 2016 to 2020, increasing from 0.27 to 1.79. Just over half of the patients achieved favourable treatment outcomes, while a significant number faced unfavourable outcomes, primarily due to loss to follow-up and death. Middle-aged males were the most affected, often presenting with comorbidities such as diabetes and HIV. These findings emphasise the critical need for enhanced monitoring, commitment from healthcare workers and family support in treatment supervision. The rising trend of pre-extensively drug-resistant tuberculosis and extensively drug-resistant tuberculosis poses a significant global threat with limited treatment options, highlighting the importance of prevention over treatment alone.

ACKNOWLEDGEMENT

Ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health (NMRR ID-23-00038-72L) and the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/22110712). The study adhered to the principles outlined in the Declaration of Helsinki and followed the guidelines set forth by the Malaysian Good Clinical Practice Guideline. No subject vulnerability was involved in the study as secondary data was used. We have no conflict of interest to be declared.

The authors would like to thank the Malaysian Association for Prevention of Tuberculosis (MAPTB) for awarding us the research grant (MAPTB/N/GAB/111904). We would also like to thank all the respective personnel from the Selangor State Health Department, Kuala Lumpur and Putrajaya State Health Department, and Institute of Respiratory Medicine, Kuala Lumpur for their assistance during data collection.

REFERENCES

1. Ministry of Health Malaysia. National Strategic Plan for Tuberculosis Control (2016-2020) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/
2. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Drug-resistant tuberculosis treatment. 2022 update [cited Apr 2023]. Available from: https://www.who.int/publications/i/item/9789240063129.
3. Almeida D, Ioerger T, Tyagi S, Li SY, Mdluli K, Andries K, et al. Mutations in pepQ confer low-level resistance to bedaquiline and clofazimine in Mycobacterium tuberculosis. Antimicrob Agents Chemother 2016; 60(8): 4590–9.
4. World Health Organization. Global Tuberculosis Report 2021 [cited Oct 2022]. Available from: https://www.who.int/publications/i/item/9789240037021.
5. World Health Organization. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis [cited Nov 2022]. Available from: https://www.who.int/publications/i/item/9789240018662.
6. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020) [cited Jan 2023]. Available from: https://iris.who.int/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1.
7. Ministry of Health Malaysia. CPG management of drug resistant TB [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG%20Management%20of%20Drug%20Resistant%20TB.pdf.
8. World Health Organization. Global Tuberculosis Report 2020 [cited Oct 2022]. Available from: https://iris.who.int/bitstream/handle/10665/336069/9789240013131-eng.pdf?sequence=1.
9. Monedero-Recuero I, Gegia M, Wares DF, Chadha SS, Mirzayev F. Situational analysis of 10 countries with a high burden of drug-resistant tuberculosis 2 years post-UNHLM declaration: progress and setbacks in a changing landscape. Int J Infect Dis 2021; 108: 557–67.
10. Ou ZJ, Yu DF, Liang YH, He WQ, Li YZ, Meng YX, et al. Trends in burden of multidrug-resistant tuberculosis in countries, regions, and worldwide from 1990 to 2017: results from the Global Burden of Disease study. Infect Dis Poverty 2021; 10(1): 24.
11. Ministry of Health Malaysia. Notifikasi dan Pelaporan Kes Drug-resistant TB (DRTB), Disease Control Division. MOH circular (ref. no.: KKM.600-1/3/66 (16)); 2020. [cited Apr 2023].
12. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009; 9(3): 153–61.
13. Spence DP, Hotchkiss J, Williams CS, Davies PD. Tuberculosis and poverty. BMJ 1993; 307(6907): 759-61.
14. Department of Statistics, Malaysia. OpenDOSM [cited Apr 2023]. Available from: http://www.dosm.gov.my/v1/index.php.
15. Amin Z, Mitiku H, Marami D, Shume T, Weldegebreal F. Magnitude of multidrug resistance and associated factors of pulmonary tuberculosis among adult smear positive patients in eastern Ethiopia. Infect Drug Resist 2021; 14: 4493–4500.
16. Al Ammari M, Al Turaiki A, Al Essa M, Kashkary AM, Eltigani SA, Ahmed AE. Drug-resistant tuberculosis in Saudi Arabia: an analysis of surveillance data 2014-2015. Antimicrob Resist Infect Control 2018; 7: 12.
17. Sambas M, Rabbani U, Al-Gethamy MMM, Surbaya SH, Alharbi FFI, Ahmad RGA, et al. Prevalence and determinants of multidrug-resistant tuberculosis in Makkah, Saudi Arabia. Infect Drug Resist 2020; 13: 4031-8.

18. Jitmuang A, Munjit P, Foongladda S. Prevalence and Factors Associated with Multidrug-Resistant Tuberculosis at Siriraj Hospital, Bangkok, Thailand. Southeast Asian J Trop Med Public Health 2015; 46(4): 697-706.
19. Goroh MMD, Rajahram GS, Avoi R, Van Den Boogaard CHA, William T, Ralph AP, et al. Epidemiology of tuberculosis in Sabah, Malaysia, 2012-2018. Infect Dis Poverty 2020; 9: 1-11.
20. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational 'how-to' practical considerations. Geneva: World Health Organization 2011. [cited August 2024]. Available from: https://iris.who.int/bitstream/handle/10665/44593/9789241501569_eng.pdf?sequence=1.
21. Al-Darraji HA, Abd Razak H, Ng KP, Altice FL, Kamarulzaman A. The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. PLoS One 2013; 8(9): e73717.
22. Wrohan I, Nguyen TA, Nguyen VN, Nguyen BH, Hoang TTT, Nguyen PC, et al. Predictors of treatment outcomes among patients with multidrug-resistant tuberculosis in Vietnam: a retrospective cohort study. BMC Infect Dis 2022; 22(1): 68.
23. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis treatment non-adherence and lost to follow up among TB patients with or without HIV in developing countries: a systematic review. Iran J Public Health 2015; 44(1): 111.
24. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Healthcare system factors influencing treatment results of MDR TB patients [cited Nov 2022]. Available from: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/mdr-tb-healthcare-factors-influencing-treatment-results.pdf.
25. Baral SC, Karki DK, Newell JN. Causes of stigma and discrimination associated with tuberculosis in Nepal: a qualitative study. BMC Public Health 2007; 7: 211.
26. Ma JB, Zeng LC, Ren F, Dang LY, Luo H, Wu YQ, et al. Treatment outcomes and risk factors of multidrug-resistant tuberculosis patients in Xi'an China, a retrospective cohort study. Infect Drug Resist 2022; 15: 4947–57.
27. Rajendran M, Zaki RA, Aghamohammadi N. Contributing risk factors towards the prevalence of multidrug-resistant tuberculosis in Malaysia: a systematic review. Tuberculosis (Edinb) 2020; 122: 101925.
28. Molla KA, Reta MA, Ayene YY. Prevalence of multidrug-resistant tuberculosis in East Africa: a systematic review and meta-analysis. PLoS One 2022; 17(6): e0270272.
29. Kaur K, Said S, Norkhadijah S, Lim PY. Risk factors of unfavourable TB treatment outcomes in Hulu Langat, Selangor. Malays J Med Health Sci 2022; 18: 52–60.
30. Johansson E, Long NH, Diwan VK, Winkvist A. Gender and tuberculosis control: perspectives on health-seeking behaviour among men and women in Vietnam. Health Policy 2000; 52(1): 33–51.
31. International Labour Organization. TRIANGLE in ASEAN Quarterly Briefing Note Malaysia July-December 2022 [cited May 2022]. Available from: https://www.ilo.org/wcmsp5/groups/public/---asia/---ro-bangkok/documents/genericdocument/wcms_614381.pdf.
32. Liew SM, Khoo EM, Ho BK, Lee YK, Mimi O, Fazlina MY, et al. Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. Int J Tuberc Lung Dis 2015; 19(7): 764–71.
33. Ministry of Education, Malaysia. Malaysia Education Statistics [cited Apr 2023]. Available from: https://www.moe.gov.my/en/muat-turun/laporan-dan-statistik/quick-facts-malaysia-education-statistics/563-quick-facts-2018-malaysia-educational-statistics/file.
34. Elmi OS, Hasan H, Abdullah S, Mat Jaeb MZ, Bin Alwi Z, Naing NN. Multidrug-resistant tuberculosis and risk factors associated with its development: a retrospective study. J Infect Dev Ctries 2015; 9(10): 1076–85.
35. Law WS, Yew WW, Chiu Leung C, Kam KM, Tam CM, Chan CK, et al. Risk factors for multidrug-resistant tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2008; 12(9): 1065–70.
36. Ministry of Health Malaysia. Management of Tuberculosis (Fourth Edition) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Main%20Banner/2021/Okt/Draft_CPGManagement_of_Tuberculosis(Fourth_Edition)_for_Reviewers.pdf.
37. Abubakar I, Story A, Lipman M, Bothamley G, van Hest R, Andrews N, et al. Diagnostic accuracy of digital chest radiography for pulmonary tuberculosis in a UK urban population. Eur Respir J 2010; 35(3): 689–92.
38. Murthy SE, Chatterjee F, Crook A, Dawson R, Mendel C, Murphy ME, et al. Pretreatment chest x-ray severity and its relation to bacterial burden in smear positive pulmonary tuberculosis. BMC Med 2018; 16(1): 73.
39. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh Jr. CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993; 328(8): 527–32.
40. Ministry of Health Malaysia. Management of Tuberculosis (Third Edition) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/attachments/8612.pdf.

Prevalence of occupational noise-induced hearing loss and its associated factors among marine technicians working on the Royal Malaysian Navy vessels

Wan Mohd Muizzuddin Wan Mohamed, MPH[1,2], Siti Hajar Adam, PhD[3], Khairul Anwar Zarkasi, PhD[3], Siti Zulaili Zulkepli, MS[4]

[1]Public Health Unit, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia, Kem Sungai Besi, Kuala Lumpur, Malaysia, [2]Institute of Underwater and Hyperbaric Medicine, 96 Hospital Angkatan Tentera, Pangkalan TLDM Lumut, Lumut, Perak, Malaysia, [3]Preclinical Department, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia, Kem Sungai Besi, Kuala Lumpur, Malaysia, [4]Department of Otorhinolaryngology, 96 Hospital Angkatan Tentera, Pangkalan TLDM Lumut, Lumut, Perak, Malaysia

ABSTRACT

Introduction: Noise-induced hearing loss (NIHL) is the second most common form of sensorineural hearing loss. It is one of the occupational health concerns worldwide with a prevalence rate of 16%. In Malaysia, there is an increasing trend of occupational NIHL prevalence encompassing agriculture, manufacturing, transportation, and construction sectors. The Malaysian Armed Forces (MAF) personnel, particularly the marine technicians of the Royal Malaysian Navy (RMN), have a heightened risk of developing NIHL due to prolonged exposure to hazardous noise levels onboard the military vessels. Previous studies involving MAF participants recorded a prevalence rate of approximately 22%. However, limited information is available regarding occupational NIHL among the RMN marine technicians. This study aimed to determine the prevalence of occupational NIHL and its associated factors among marine technicians working on the RMN vessels.

Materials and Methods: A cross-sectional study was conducted among 127 randomly selected participants among marine technicians working on RMN vessels stationed at the Lumut Naval Base, Perak, Malaysia. The research instruments were questionnaires that contained information about sociodemographic, socioeconomic, occupational characteristics, and lifestyle behaviours, followed by a pure tone audiometric (PTA) assessment. Diagnosis of NIHL was made when the hearing threshold was ≥25 dB at 3 kHz to 6 kHz, with a recovery at 8 kHz on PTA.

Results: The participants' median age was 32 years (interquartile range=27–37 years). The prevalence of occupational NIHL was 29.9% (95% CI=22.1–38.7). Factors associated with occupational NIHL on unadjusted regression analysis include age >30 years (OR=2.56, p=0.0185), middle household income (OR=2.76, p=0.0227), military rank especially the warrant officer (OR=7.12, p=0.0038), and length of service ≥15 years (OR=2.40, p=0.0246). After adjusting for ethnicity, smoking status, types of vessels, and participation in noise-related leisure activities, middle household income (OR=3.15, 95% CI=1.29–7.87, p=0.0121) and warrant officer (OR=4.38, 95% CI=1.08–20.52, p=0.0384) remained as significant predictors for occupational NIHL in this population.

Conclusion: In this study, the marine technicians working on board the RMN vessels had a higher prevalence of occupational NIHL compared to the prevalence among other MAF personnel as well as the global data. In addition, the probabilities of having occupational NIHL were significantly higher for middle-income technicians and those who ranked as warrant officers. These findings highlight the need for routine audiometric assessment and adoption of hearing conservation initiatives for individuals at high risk within this occupational cohort.

KEYWORDS:
Noise-induced hearing loss, occupational NIHL, marine technicians, Royal Malaysian Navy, Malaysian Armed Forces

INTRODUCTION

Noise-induced hearing loss (NIHL) affects approximately 5% of the global population, and it is the second most common type of sensorineural hearing loss.[1] Additionally, about 16% of hearing loss in adults is caused by NIHL.[2] Excessive exposure to loud noise that occurs at workplaces, known as occupational NIHL, usually affects those who work in the manufacturing, construction, mining, and military sectors.[3,4] The occurrence of NIHL is caused by continuous exposures to loud sounds measuring >85 decibels (dB) for more than eight hours per day or a single exposure to an impulse sound of >140 dB without any hearing protection.[5] The affected individuals often complain of ear-related symptoms such as temporary or permanent hearing loss and tinnitus, as well as impaired functioning and quality of life, including sleep deprivation and reduced work performance, potentially leading to psychological stress.[6] Apart from prolonged exposures to loud noise, other identified risk factors of occupational NIHL comprised age, male gender, duration of employment, and active cigarette smoking.[7]

This article was accepted: 16 September 2024
Corresponding Author: Khairul Anwar Zarkasi
Email: khairul.anwar@upnm.edu.my

In Malaysia, noise exposure at the workplace is regulated under the Occupational Safety and Health (Noise Exposure) Regulations 2019 which limits the daily noise exposure to 85 dB(A), a daily dose of self-noise at 100%, maximum noise pressure at 115 dB(A) at any time, and peak sound pressure level at 140 dB(C).[8] The prevalence of occupational NIHL among Malaysian workers has seen a dramatic increase. For the past decade, the number of occupational NIHL has risen from 358 reported cases in 2014 to 5,101 cases in 2023, equivalent to a staggering increase of 1,325%.[9,10] However, these data did not include individuals who were serving in the military, rather they were aggregated from other sectors such as agriculture, manufacturing, transportation, and construction.[11] Similar to industrial workers, military personnel are regularly exposed to high noise levels above 85 dB from their daily routine which involves handling sophisticated military vehicles and machines, weapon-firing practices, as well as the usage of explosions.[12,13] Out of various military branches and ranks, marine technicians working on board navy vessels are particularly among those who have high exposure to loud noises. This is because the vessels constantly have higher noise levels compared to the recommended upper-limit values when they are being operated at sea, especially in the enclosed space of the engine room where marine technicians typically work.[14] According to a recently published paper, the noise levels onboard a navy vessel in various spaces on all decks exceeded the international standards set by the International Maritime Organization (IMO), Det Norske Veritas (DNV), and China Classification Society (CCS).[15] The maximum sound level was recorded in the engine room and the engine control room at 175.2 dB (+59.3%) and 112.7 dB (+32.6%), respectively, which were comparatively higher than the standard limits.[15] Meanwhile, the maximum sound levels in other parts of the vessel ranged from 70.5–85.2 dB or approximately 0.72%–21.7% higher compared to the standard limits.[15]

The roles of the Royal Malaysian Navy (RMN) marine technicians include operating and maintaining the engine and drive systems, as well as monitoring the auxiliary, power generation, and distribution systems of the vessels. To complete these tasks, marine technicians are often required to be present in the engine room for approximately 4 hours per shift. This arrangement leads to significant exposure to loud noises with a subsequently marked increase in their risk of contracting NIHL since the engine room had the loudest noise of >100 dB as compared to the other parts of a vessel.[14,16] Due to the difficulty in implementing engineering controls such as modification using insulation or barrier towards the noise source on the vessel, workers at risk of occupational NIHL are expected to strictly adhere to the usage of personal hearing protectors (PHP) during duty. However, about one in five military personnel did not use PHP,[17] with one in three personnel reporting that they had never received guidance on how to properly use the equipment.[18]

At present, the information regarding occupational NIHL among Malaysian military personnel is scarce, with only two studies conducted so far, involving technicians in the Royal Malaysian Air Force (RMAF) as well as divers and non-divers of the RMN, respectively.[19,20] Among the RMAF technicians, the overall NIHL prevalence was 24.2% with loud-sound leisure activities and a history of tinnitus as its significant associated factors.[19] As for the RMN divers and non-divers, NIHL was associated with older age and longer duration of service, with an overall prevalence of 18.9%.[20] Given that the occupational NIHL is understudied among the Malaysian Armed Forces (MAF) personnel, investigation regarding the presence of this preventable disease especially among the RMN marine technicians is crucial and of utmost importance as the initial step in planning for prevention strategies. Therefore, the current study aimed to determine the prevalence of occupational NIHL and its associated factors among the marine technicians working on board the RMN vessels.

MATERIALS AND METHODS

Study design and setting

A cross-sectional study was conducted among marine technicians working on the RMN vessels stationed at the Lumut Naval Base, Perak Malaysia from February to April 2023. Lumut Naval Base is strategically situated on the west coast of Peninsular Malaysia, approximately 160 kilometres from Kuala Lumpur. It lies along the eastern coast of the Malacca Strait, providing easy access to important maritime routes and serving as a crucial operational hub for the RMN. The base accommodates various RMN units such as Western Fleet Command, Naval Education and Training Command, Naval Special Forces, Naval Air, Diving Headquarters and Mine Warfare, Navy Provost Unit, and Malaysian Army Unit which encompasses the 96 Armed Forces Hospital. It also houses various naval facilities, including berths for warships, maintenance and repair facilities, administrative buildings, training facilities, and support infrastructure.

Ethical approval

This study had been approved by the UPNM Research Ethics Committee (Ethics No.: UPNM (FPKP) 14.01/02) and the Clinical Research Committee of the Malaysian Armed Forces Health Services (Ethics No.: PKAT/JKE/40-08).

Sample size and sampling technique

There was a total of 238 marine technicians in the Lumut Naval Base. The inclusion criteria for this study include all marine technicians of any rank with normal preliminary otoscope findings and who were actively serving in the RMN vessels stationed at the base during the study period. Marine technicians who had been drafted out of vessels, those with existing hearing loss other than NIHL, and a history of recent ear infections, trauma, or surgeries were excluded. Based on the NIHL prevalence of 31.4% as reported by Irgen-Hansen et al. (2015), absolute precision at 5%, and 95% confidence interval, the sample size calculated using "Sample Size for Frequency in a Population" (https://www.openepi.com/) was 139.[21,22] The name list containing all marine technicians in the base was assigned a number, followed by subject selection using a random number generator to ensure that each personnel had an equal chance of being included. A total of 127 eligible subjects agreed to participate in this study with a response rate of 91.4%.

Tools

In this study, data on sociodemographic, lifestyle, and occupational characteristics were obtained from participants.[19] Sociodemographic information encompassed

age, ethnicity, education level, and household income, while lifestyle behaviours included smoking, alcohol consumption, and participation in noise-exposed leisure activities. Household income was further divided into low-income (<RM 3,660) and middle-income (RM 3,660–7,639) categories according to the report by the Department of Statistics Malaysia for the State of Perak.[23] Participation in noise-exposed leisure activities included attending night clubs, involvement in motorsports and shooting clubs, listening to music in vehicles with loud sound systems, listening to music using headsets or earphones at high volume, and attending concerts.[19] Participants could also choose none or individually mention the type of noise-exposed leisure activities if they were not listed as options in the questionnaire. Meanwhile, the occupational characteristics recorded comprised rank, length of service, and types of vessels.

Hearing assessments and NIHL diagnosis

Hearing assessments were conducted using the GSI 61 Clinical Audiometer (Grason-Stadler, Minnesota, USA) in the Otorhinolaryngology (ORL) clinic at 96 Hospital Angkatan Tentera located within the Lumut Naval Base. Before the test, all participants were instructed to avoid exposure to any loud noise for at least 16 hours. Participants underwent testing in a soundproof booth with a background noise level below 25 dB(A), with each ear tested independently. Audiometric assessments followed the Hughson-Westlake method, measuring pure tone air conduction.[24] Starting at 1 kHz with an intensity of 30 dB, participants signalled sound detection via a button press. The sound intensity was decreased gradually by 10 dB until no response was elicited, followed by 5 dB gradual increments until response reoccurred. This procedure was repeated three times to identify the threshold, which was defined as the lowest intensity level that elicited two responses out of three presentations. Following the completion of lower frequency testing, the audiometry procedure returned to 1 kHz for rechecking before continuing to higher frequencies.[24] Diagnosis of NIHL is made according to the American College of Occupational and Environmental Medicine's criteria, which requires a threshold of ≥25 dB at 3 kHz, 4 kHz, and 6 kHz, with subsequent recovery at 8 kHz.[3]

Statistical analysis

Data were analysed using SPSS® Statistics® v26 (IBM Corp., New York, USA) and R v4.3.1 (Bell Labs., New Jersey, USA) in the RStudio v2023.12.1 environment (Posit Software, Massachusetts, USA). Continuous data were presented as median and interquartile range following non-normal distribution assessed by the Kolmogorov-Smirnov test, whereas categorical data were presented as counts and percentages. Factors associated with occupational NIHL were initially examined by Pearson χ^2 or Fisher exact tests, followed by further analysis using Firth bias-reduced logistic regression with and without covariates adjustments.[25] This method was applied to reduce the inflated bias caused by covariates with zero counts in the contingency table. Significant results were determined when $p<0.05$ (two-sided).

RESULTS

The socio-demographic characteristics are listed in Table I. The median age of the participants was 32 years, and they mostly came from the Malay ethnicity (n=121, 95.3%). There was a higher proportion of the participants who had a secondary education level (n=82, 64.6%) while the rest had a tertiary education level (n=45, 35.4%). The median household income was RM 2,600. Most of the participants denied alcohol consumption (n=125, 98.4%) or participation in noise-related leisure activities (n=103, 81.1%). Over half of the participants were self-identified as active smokers (n=69, 54.3%).

In terms of military rank, approximately half of the participants were junior able (n=66, 52.0%), followed by petty officer (n=51, 40.2%) and warrant officer (n=10, 7.9%). Most of the participants (n=59, 46.5%) were stationed at the support flotilla, followed by the attack flotilla (n=48, 37.8%), patrol flotilla (n=18, 14.2%), and training flotilla (n=2, 1.6%). The median length of service among participants was 11 years.

Out of 127 subjects, 38 participants were diagnosed with occupational NIHL, with a prevalence rate of 29.9% (95% CI=22.1–38.7) as shown in Table II.

Factors associated with occupational NIHL among the RMN marine technicians are listed in Table III. Based on the Pearson χ^2 test, age (p=0.0183), household income (p=0.0198) and length of service (p=0.0233) had a significant association with occupational NIHL, whereas the education level, smoking status, and participation in noise-related leisure activities were not associated with NIHL. On the Fisher exact test, the military rank (p=0.0120) also showed a significant association with occupational NIHL but not for other variables including ethnicity, alcohol intake, and type of vessels.

Predictors of occupational NIHL among the RMN marine technicians are presented in Table IV. Unadjusted logistic regression analysis (model 1) revealed four variables significantly associated with occupational NIHL. These include age >30 years (OR=2.56, 95% CI=1.17–5.88), middle household income of ≥RM 3,660 (OR=2.76, 95% CI=1.15–6.61), military rank especially the warrant officer (OR=7.12, 95% CI=1.87–32.43), and length of service of ≥15 years (OR=2.40, 95% CI=1.12–5.22) (all $p<0.05$).

In model 2, logistic regression was performed for each predictor with adjustment for ethnicity, smoking status, and type of vessels, since these three variables showed $p<0.2$ on the initial analysis using Pearson χ^2 or Fisher exact tests. Following covariates adjustment, two variables retained a significant association with occupational NIHL, including middle household income (OR=3.21, 95% CI=1.31–8.05) and warrant officer (OR=4.48, 95% CI=1.11–21.04) (all $p<0.05$) (Table IV).

Additional adjustment for noise-related leisure activities was performed in model 3 to further confirm the association of household income and military rank on occupational NIHL. The results showed that middle household income had a 3.15 times increased probability of having occupational NIHL as compared to low household income (95% CI=1.29–7.87, p=0.0112). Additionally, warrant officers had a 4.38 times

Table I: Baseline characteristics of the study population

Characteristics	Frequency (%) (n=127)	Median (IQR)
Age (years)		32 (27–37)
Ethnicity		
Non-Malay	6 (4.7)	
Malay	121 (95.3)	
Education level		
Secondary	82 (64.6)	
Tertiary	45 (35.4)	
Household income (RM)		2,600 (2,000–3,300)
Smoking status		
Non-smoker	58 (45.7)	
Active smoker	69 (54.3)	
Alcohol intake		
No	125 (98.4)	
Yes	2 (1.6)	
Noise-related leisure activities		
No	103 (81.1)	
Yes	24 (18.9)	
Military rank		
Junior able	66 (52.0)	
Petty officer	51 (40.2)	
Warrant officer	10 (7.9)	
Types of vessels		
Attack flotilla	48 (37.8)	
Patrol flotilla	18 (14.2)	
Support flotilla	59 (46.5)	
Training flotilla	2 (1.6)	
Length of service (years)		11 (6–17)

Continuous data are presented as median (IQR) and categorical data are presented as count (percentage).

Table II: Prevalence of occupational NIHL among the RMN marine technicians

Occupational NIHL	Frequency (%) (n=127)	95% CI (%)
Yes	38 (29.9)	22.1–38.7
No	89 (70.1)	61.3–77.9

Abbreviations: CI (confidence interval), NIHL (noise-induced hearing loss), RMN (Royal Malaysian Navy).

higher probability of having occupational NIHL than junior able (95% CI=1.08–20.52, p=0.0384) (Table IV).

DISCUSSION

The current study found that approximately one in every three marine technicians (29.9%) working on board the RMN vessels suffered from occupational NIHL, which is markedly higher than the 5% global prevalence.[1] This is not surprising since military personnel are regularly exposed to a higher degree of noise compared to the general population. The source of noise in the military settings includes military weapon systems that could generate more than 140 dB peak sound pressure level (dBP) with some weapon classes generating even higher noise of more than 180 dBP.[26] As for the marine technicians, the sound generated inside the engine room where they typically work is within the range of 108–118 dB(A),[26] significantly higher than the cut-off criteria of noise exposure in NIHL diagnosis.[5] The prevalence of occupational NIHL among RMN marine technicians in this study is comparatively lower compared to previously reported data from the foreign military. For instance, a study among 605 Royal Norwegian Navy personnel found that the total prevalence of hearing loss was 31.4% with the highest recorded prevalence among the engine room workers at 38.0%.[22] Similarly, among 150 personnel of the Belgian Armed Forces, the prevalence of hearing loss was 62.7% whereas the highest percentage was also recorded among the navy at approximately 80%.[27] However, both studies included all types of hearing loss and did not focus specifically on occupational NIHL which could explain the higher prevalence observed.

In Malaysia, there were two reported studies regarding the prevalence of occupational NIHL among military personnel. The overall prevalence of occupational NIHL was 24.2% among 263 RMAF aircraft technicians and 18.9% among 233 RMN personnel,[19,20] both of which were comparatively lower than the prevalence observed in the current study. The differences in the prevalence could be explained by the variation in the populations being studied that was closely related to their work environment. In the current study,

Table III: Factors associated with occupational NIHL among the RMN marine technicians

Parameters	Occupational NIHL		p-value
	Yes (n=38)	No (n=89)	
Age[a]			0.0183*
≤30 years	11 (19.3)	46 (80.7)	
>30 years	27 (38.6)	43 (61.4)	
Ethnicity[b]			0.1775
Non-Malay	0 (0.0)	6 (100.0)	
Malay	38 (31.4)	83 (68.6)	
Education level[a]			0.8283
Secondary	24 (29.3)	58 (70.7)	
Tertiary	14 (31.1)	31 (68.9)	
Household income[a]			0.0198*
Low	25 (25.0)	75 (75.0)	
Middle	13 (48.1)	14 (51.9)	
Smoking status[a]			0.1561
Non-smoker	21 (36.2)	37 (63.8)	
Active smoker	17 (24.6)	52 (75.4)	
Alcohol intake[b]			1.0000
No	38 (30.4)	87 (69.6)	
Yes	0 (0.0)	2 (100.0)	
Noise-related leisure activities[a]			0.9286
No	31 (30.1)	72 (69.9)	
Yes	7 (29.2)	17 (70.8)	
Military rank[b]			0.0120*
Junior able	15 (22.7)	51 (77.3)	
Petty officer	16 (31.4)	35 (68.6)	
Warrant officer	7 (70.0)	3 (30.0)	
Types of vessels[b]			0.1033
Attack flotilla	15 (31.3)	33 (68.8)	
Patrol flotilla	7 (38.9)	11 (61.1)	
Support flotilla	14 (23.7)	45 (76.3)	
Training flotilla	2 (100.0)	0 (0.0)	
Length of service[a]			0.0233*
<15 years	17 (22.4)	59 (77.6)	
≥15 years	21 (41.2)	30 (58.8)	

Data were analysed using [a]Pearson χ^2 and [b]Fisher exact tests. *Significant results at p<0.05. Abbreviations: IQR (interquartile range), NIHL (noise-induced hearing loss), RMN (Royal Malaysian Navy).

Table IV: Predictors of occupational NIHL among the RMN marine technicians

Predictors	Model 1 OR (95% CI)	p-value	Model 2 OR (95% CI)	p-value	Model 3 OR (95% CI)	p-value
Age						
≤30 years	1 (Ref.)	-	1 (Ref.)	-	1 (Ref.)	-
>30 years	2.56 (1.17–5.88)	0.0185*	1.81 (0.78–4.38)	0.1705	1.79 (0.77–4.31)	0.1759
Household income						
Low	1 (Ref.)	-	1 (Ref.)	-	1 (Ref.)	-
Middle	2.76 (1.15–6.61)	0.0227*	3.21 (1.31–8.05)	0.0112*	3.15 (1.29–7.87)	0.0121*
Military rank						
Junior able	1 (Ref.)	-	1 (Ref.)	-	1 (Ref.)	-
Petty officer	1.54 (0.68–3.51)	0.2954	1.10 (0.45–2.63)	0.8329	1.09 (0.45–2.60)	0.8467
Warrant officer	7.12 (1.87–32.43)	0.0038*	4.48 (1.11–21.04)	0.0355*	4.38 (1.08–20.52)	0.0384*
Length of service						
<15 years	1 (Ref.)	-	1 (Ref.)	-	1 (Ref.)	-
≥15 years	2.40 (1.12–5.22)	0.0246*	1.73 (0.78–3.86)	0.1756	1.71 (0.77–3.81)	0.1865

Data were analysed using Firth bias-reduced logistic regression. Model 1: no covariate adjustment, Model 2: adjusted for ethnicity, smoking status, and types of vessels, Model 3: adjusted for covariates in Model 2 + noise-related leisure activities. *Significant results at p<0.05. Abbreviations: CI (confidence interval), NIHL (noise-induced hearing loss), OR (odds ratio), Ref. (reference), RMN (Royal Malaysian Navy).

marine technicians operated within the confined spaces of RMN vessels, whereas the RMAF aircraft technicians mostly worked on open spaces such as airstrips or hangars. Compared to open spaces, confined spaces like the engine room with limited entry and exit openings are more hazardous.[28] Sounds originating from the generators, engines, and other machinery would undergo reverberation from the walls causing sound amplification and potential long-term effects on hearing.[29] Although the other study was also conducted among RMN personnel,[20] the study population was not focused on marine technicians. Rather, it included various roles in the RMN broadly classified into those who were in the diving and non-diving units.[20] Similar to marine technicians, divers are also exposed to high noise levels between 88.3–91.8 dB(A) from breathing apparatus and communication devices.[30] However, these noises are generally lower than the 104 dB(A) produced within engine room,[14] which could explain the higher prevalence of occupational NIHL in the current study.

To uncover the associated factors of occupational NIHL among RMN marine technicians, we analysed several parameters including the sociodemographic and socioeconomic characteristics (i.e., age, ethnicity, education level, and household income), lifestyle characteristics (i.e., smoking status, alcohol intake, and participation in the noise-related leisure activities), as well as occupational characteristics (i.e., military rank, types of vessels, and length of service). Data analysis without covariate adjustments revealed that four parameters showed significant associations with occupational NIHL in the current study, comprising age >30 years, middle household income of ≥RM 3,660, military rank especially the warrant officer, and length of service ≥15 years. Upon further analysis with covariate adjustments, only two parameters retained a significant association with occupational NIHL including higher household income and higher military rank.

Higher household income was associated with 3.15 times increased probability of having occupational NIHL in the current study. This is in contrast with findings from previously published papers involving working adult populations. For instance, a study among 16,078 participants of the National Health and Nutrition Examination Survey (NHANES) in the United States indicated that there was no association between income and occupational NIHL (OR=1.02, p=0.755).[31] Similarly, income had no association with occupational NIHL (OR=0.88, p=0.230) as reported in another study involving 10,850 participants of the Korea National Health and Nutrition Examination Survey (KNHANES).[32] Although there was a significant association between income and high-frequency hearing loss, data from 3,999 participants of the Canadian Health Measures Survey (CHMS) showed that the prevalence of occupational hearing loss was lower in the middle and high-income categories compared to low-income group (31.1%, 28.6%, and 41.0%, respectively, p<0.05).[33]

At present, there is no data regarding the association between household income and occupational NIHL in military settings. However, the association between household income and NIHL in the current study has a similar direction when compared to previous studies using non-working populations. For example, a study among 1,845 South Korean adolescents aged 12–19 years found that those who came from a high household income family had 1.39 times increased odds of having NIHL (95% CI=1.00–1.99, p<0.05).[34] Meanwhile, among 245 Jordanian university students, hearing symptoms including hearing loss and usage of hearing aids were more prevalent among individuals from above-average income families compared to those from average and below-average income families (57.6%, 33.3%, and 22.2%, respectively, p=0.017).[35] Individuals who have better socioeconomic status might not need to pursue part-time jobs and would have more free time to engage in loud noise-related leisure activities.[35] They might also have higher purchasing power and could afford to purchase personal music devices, smartphones, or sound systems,[34] which further increases their exposure to loud noises, resulting in a higher risk of NIHL. However, there was no association between participation in noise-related leisure activities with occupational NIHL found in the current study.

Higher military rank, specifically the warrant officer, is associated with a 4.38 times higher probability of having occupational NIHL as observed in the present study. On the contrary, Kim et al. (2021) reported that among 13,470 Republic of Korean military personnel, the enlisted soldiers, of lower ranks, had 1.92–2.58 higher odds of having occupational NIHL as compared to the warrant and commissioned officers (p<0.05).[36] The increased probability for occupational NIHL among higher military ranks in the present study could be explained by military personnel's composition and allocation for each flotilla. The number of warrant officers for marine technicians in each RMN vessel is limited to one or two depending on the vessel's size. If repair is required during sailing, the warrant officer will remain stationed within the engine room for the entire duration of the repair process. This is because the warrant officer will be the most knowledgeable and experienced in handling the repair. Comparatively, the lower-ranked personnel will have the flexibility to take turns in performing the repair procedure. Consequently, the warrant officers would have more prolonged exposure to the noise in the engine room, thus, increasing their risk for occupational NIHL.

Several limitations have been identified in this study. First, we did not measure the level of noise exposure using a personal dosimeter or noise mapping for each flotilla type using a sound level meter due to cost restrictions. Consequently, we also did not assess the usage of PHP such as earplugs and earmuffs to avoid misunderstanding among the marine technicians that they were being evaluated on competency and discipline in following the standard operating procedures as implemented by the RMN that could affect the response rate. Finally, the baseline audiogram data for each participant were unavailable for comparison. Therefore, we could not confidently determine whether the occupational NIHL was present before or after the participants had started working on board the RMN vessels. Since participants were randomly selected and the distribution of flotilla types as well as ranks of the marine technicians are similar across other Malaysian naval bases, the results from this study can be applied to the whole population of marine technicians serving on board the RMN vessels.

CONCLUSION

The marine technicians working on board the RMN vessels had a higher prevalence of occupational NIHL compared to the prevalence among other Malaysian Armed Forces (MAF) personnel as well as the global data. Higher household income and higher military rank are the associated factors and significant predictors for occupational NIHL among RMN marine technicians. These findings may necessitate regular audiometric testing as well as the implementation of a hearing conservative programme, especially for individuals at high risk.

ACKNOWLEDGEMENT

We would like to thank the Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (UPNM) and Military Health Services, Malaysian Armed Forces (MAF) for providing the approval to conduct this research. We extend our utmost gratitude to the Otorhinolaryngology Clinic's staff and personnel of the 96 Hospital Angkatan Tentera including the audiologists who assisted with data collection and performed the pure tone audiometry tests. The publication fee was funded by the Research and Innovation Management Centre, UPNM.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Natarajan N, Batts S, Stankovic KM. Noise-induced hearing loss. J Clin Med 2023; 12(6): 2347.
2. Śliwińska-Kowalska M, Zaborowski K. WHO environmental noise guidelines for the European region: A systematic review on environmental noise and permanent hearing loss and tinnitus. Int J Environ Res Public Health 2017; 14(10): 1139.
3. Mirza R, Kirchner DB, Dobie RA, Crawford J. Occupational noise-induced hearing loss. J Occup Environ Med 2018; 60(9): e498–501.
4. Themann CL, Masterson EA. Occupational noise exposure: A review of its effects, epidemiology, and impact with recommendations for reducing its burden. J Acoust Soc Am 2019; 146(5): 3879.
5. Yong JSE, Wang DY. Impact of noise on hearing in the military. Mil Med Res 2015; 2: 6.
6. Graydon K, Gunasekera H, Miller H, Waterworth C. Global burden of hearing impairment and ear disease. J Laryngol Otol 2019; 133(1): 18–25.
7. Halim I, Azizul I, David CCH, Hanis A, Hafiz B, Naiemy R, et al. Noise-induced hearing loss among manufacturing factory workers in Kuching, Sarawak: Prevalence and associated risk factors. Med J Malaysia 2023; 78(5): 559–65.
8. Ministry of Human Resources. Occupational Safety and Health (Noise Exposure) Regulations 2019. Putrajaya: Ministry of Human Resources; 2019.
9. Social Security Organisation. 2014 Annual Report. Kuala Lumpur: Social Security Organisation; 2014.
10. Bernama. DOSH records over 5,000 cases of hearing problems due to occupational noise: The New Straits Times; [updated 17 August 2023, cited 1 March 2024]. Available from: https://www.nst.com.my/news/nation/2023/08/944121/dosh-records-over-5000-cases-hearing-problems-due-occupational-noise.
11. Department of Statistics Malaysia. National Occupational Accident and Disease Statistics 2021; [updated 31 December 2021, cited 1 March 2024]. Available from: https://www.ilmia.gov.my/index.php/en/bda-noa.
12. Collée A, Legrand C, Govaerts B, Van Der Veken P, De Boodt F, Degrave E. Occupational exposure to noise and the prevalence of hearing loss in a Belgian military population: A cross-sectional study. Noise Health 2011; 13(50): 64–70.
13. Nair S, Kashyap RC. Prevalence of noise induced hearing loss in Indian Air Force personnel. Med J Armed Forces India 2009; 65(3): 247–51.
14. Oldenburg M, Felten C, Hedtmann J, Jensen HJ. Physical influences on seafarers are different during their voyage episodes of port stay, river passage and sea passage: A maritime field study. PLoS One 2020; 15(4): 1–12.
15. Ibrahim F, Abu Zarim MAUA, Razali MN, Mat Radzi Z, Zainal Abidin N, Ahmad MA, et al. Noise level analysis onboard a Vessel X during sailing at sea. Zulfaqar J Def Sci Eng Technol 2023; 6(1): 1–7.
16. Kaerlev L, Jensen A, Nielsen PS, Olsen J, Hannerz H, Tüchsen F. Hospital contacts for noise-related hearing loss among Danish seafarers and fishermen: A population-based cohort study. Noise Health 2008; 10(39): 41–5.
17. Luha A, Kaart T, Merisalu E, Indermitte E, Orru H. Hearing problems among the members of the defence forces in relation to personal and occupational risk factors. Mil Med 2020; 185(11–12): e2115–23.
18. Heupa AB, de Oliveira Gonçalves CG, Coifman H. Effects of impact noise on the hearing of military personnel. Braz J Otorhinolaryngol 2011; 77(6): 747–53.
19. Zamri MD, Anita AR, Azuhairi AA, Haizar MH, Mariah H. Predictors of aircraft related noise induced hearing loss (NIHL) among technicians in Royal Malaysian Air Force (RMAF). Int J Public Heal Clin Sci 2017; 4(3): 120–30.
20. Ahmad MA. A Study on Prevalence of Hearing Impairment and Ear Diseases among Navy Personnel of the Royal Malaysian Navy, Lumut, Perak. Universiti Sains Malaysia; 2011.
21. Sullivan KM, Dean A, Soe MM. OpenEpi: A web-based epidemiologic and statistical calculator for public health. Public Health Rep 2009; 124(3): 471–4.
22. Irgens-Hansen K, Sunde E, Bråtveit M, Baste V, Oftedal G, Koefoed V, et al. Hearing loss in the Royal Norwegian Navy: A cross-sectional study. Int Arch Occup Environ Health 2015; 88(5): 641–9.
23. Department of Statistics Malaysia. Household Income and Basic Amenities Survey Report by State and Administrative District - Perak (2019). Putrajaya: Ministry of Economy; 2020.
24. Hughson W, Westlake HD. Manual for program outline for rehabilitation of aural casualties both military and civilian. Trans Am Acad Ophthalmol Otolaryngol 1944; 48(Suppl): 1–15.
25. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med 2002; 21(16): 2409–19.
26. Jokel C, Yankaskas K, Robinette MB. Noise of military weapons, ground vehicles, planes and ships. J Acoust Soc Am 2019; 146(5): 3832–8.
27. Orru H, Luha A, Pindus M, Jõgeva R, Vahisalu M, Lekk U, et al. Hearing loss among military personnel in relation to occupational and leisure noise exposure and usage of personal protective equipment. Noise Health 2020; 22(107): 90–8.
28. Selman J, Spickett J, Jansz J, Mullins B. Confined space rescue: A proposed procedure to reduce the risks. Saf Sci 2019; 113: 78–90.
29. Aretz M, Orlowski R. Sound strength and reverberation time in small concert halls. Appl Acoust 2009; 70(8): 1099–110.
30. Nedwell JR, Mason TI, Collett AG, Gardiner RWK. Noise exposure of commercial divers in the Norwegian sector of the North Sea. Undersea Hyperb Med 2015; 42(2): 151–8.
31. Sun R. Occupational and Socioeconomic Risk Factors of Noise-induced Hearing Loss. Yale University; 2022.

32. Lee HJ, Lee J, Yoon C, Park Y, Joo YH, Park JO, et al. Association of dietary factors with noise-induced hearing loss in Korean population: A 3-year national cohort study. PLoS One 2022; 17(12): e0279884.
33. Feder K, Michaud D, McNamee J, Fitzpatrick E, Davies H, Leroux T. Prevalence of hazardous occupational noise exposure, hearing loss, and hearing protection usage among a representative sample of working Canadians. J Occup Environ Med 2017; 59(1): 92-113.
34. Kim SH, Cha ES, Cha HE, Song JJ, Chae SW. Prevalence and clinical aspects of hearing loss among the South Korean adolescent: Data from a population-based study. Int J Pediatr Otorhinolaryngol 2020; 128: 109698.
35. Alnuman N, Ghnimat T. Awareness of noise-induced hearing loss and use of hearing protection among young adults in Jordan. Int J Environ Res Public Health 2019; 16(16): 2961.
36. Kim HJ, Oh SY, Won SY, Kim HJ, Kim TK, Ko BC, et al. Associations between earplug use and hearing loss in ROK military personnel. BMJ Mil Heal 2021; 167(6): 398–401.

Correlation between auditory brainstem responses, hyperacusis, and severity of autism spectrum disorder in young children with normal hearing at a tertiary referral center in Indonesia

Margaretta Simamora, MD[1], Semiramis Zizlavsky, MD[1], Tri Juda Airlangga Hardjoprawito, MD[1], Tjhin Wiguna, PhD[2], Bernie Endyarni Medise, MD[3], Retno Wibawanti, MD[4]

[1]Department of Otorhinolaryngology Head and Neck Surgery (ORL-HNS), Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia, [2]Department of Psychiatry, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia, [3]Department of Pediatric, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia, [4]Department of Community Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

ABSTRACT

Introduction: Autism spectrum disorder (ASD) is a complex condition impacting social communication, behavior, and interests. ASD affects 1 in 100 children globally, with a higher prevalence in boys. Auditory disorders, including hyperacusis, are common in ASD, yet the correlation between Auditory Brainstem Response (ABR) wave latencies and ASD severity, especially with hyperacusis, is under-researched. This study investigates ABR wave latencies in ASD children, exploring their relationship with ASD severity and h as a potential screening tool for ASD. Early diagnose and therapy could enhance the quality of life in ASD patients.

Materials and Methods: A cross-sectional study was conducted by recruiting normal-hearing children aged 3-8 years old with ASD presenting to a national referral ENT clinic between October and December 2023. The severity of ASD was assessed using the Childhood Autism Rating Scale (CARS), while hyperacusis was diagnosed using Modified Check List for Autism in Toddlers, Revised (M-CHAT-R).

Results: A total of 26 children with ASD, 23 of whom were male (88%), aged 3-8 years, were included in the analyses. Among these children, 18 (69.2%) had hyperacusis. Analysis of ABR click revealed a prolonged interpeak latency wave I and III (88.5%), followed by a prolonged latency in wave III (42.3%) and V (21.2%). Neither ABR wave latencies nor hyperacusis were correlated with the severity of ASD, although there was a marginally significant association between wave III latency and CARS score in the left ear (r=0.359, p=0.072). However, wave V latency and interpeak wave I-V latency were significantly longer in children without hyperacusis (right ear: p=0.042 and p=0.050; left ear: p=0.005 and p=0.004), while interpeak wave III-V only in the left ear (p=0.006) and wave III only in the right ear (p=0.029). Conclusion: There was no significant correlation between ABR wave latencies or hyperacusis and the severity of ASD, while ABR wave latencies were generally longer in children without hyperacusis. Further large studies involving a broader spectrum of children with ASD are warranted to confirm our findings.

KEYWORDS:
Autism spectrum disorder, brainstem evoked response audiometry, hyperacusis

INTRODUCTION

ASD is a heterogeneous condition impacting social communication deficits, repetitive behavior disorders, and limited interests.[1] According to the World Health Organization, about 1 in 100 children were affected by autism spectrum disorder (ASD) worldwide, with boys at a four-fold increased risk than girls. In the US, ASD is about 18.5 cases per 1000 children, or 1 in 54 children.[2] Indonesian data is limited but tertiary care hospital reported that ASD constitute nearly 10% of pediatric outpatients aged 18-48 months.[3] ASD are more prone to auditory disorders, including hyperacusis which could be the sign of auditory pathway disturbance or sign of abnormalities in the limbic system , which significantly impacts their quality of life.[4]

ASD diagnosed Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). However, diagnosis is often delayed, with an average of four years old, despite early symptoms onset.[5] This puts the children at higher risks of morbidity as prompt intensive treatments for example habituation training, cognitive behavioural therapy (CBT), noise-attenuated headphones, and medication such as risperidone that may induce long-term benefits for the children's social and life quality.[6,7] Currently, auditory brainstem response (ABR) testing is being explored as a potential diagnostic tool for ASD.[8] Studies have shown prolonged ABR wave latencies in ASD, particularly in waves III, V, and interpeak interval, suggesting its diagnostic value.[8,9] Despite this, evidence is lacking on ABR characteristics across the ASD spectrum and its correlation with hyperacusis.

This article was accepted: 16 September 2024
Corresponding Author: Semiramis Zizlavsky
Email: semiramiszizlavsky@gmail.com

Therefore, this study aims to characterize ABR wave latencies in children with ASD and correlate its findings with ASD severity and explore the association between ABR wave latencies and hyperacusis in children with ASD.

MATERIALS AND METHODS

This study was an analytical cross-sectional study involving children aged 3-8 years old diagnosed with ASD according to the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and a national guideline (Pedoman Penggolongan dan Diagnosa Gangguan Jiwa III) presenting to our outpatient clinic between October and December 2023.[9]

The sample size was calculated using a sampling formula, with an additional 10% added to account for potential dropouts, resulting in a total of 26 patients.[10] To control for potential confounders, we only included children with normal hearing function, as defined by a normal tympanometry and distortion product otoacoustic emission finding, and a normal hearing threshold prediction of 20 dB from ABR click and 500 Hz tone burst. Children with known neurological disabilities e.g., cerebral palsy, Down syndrome, or epilepsy were excluded.

The included children were tested for ABR click and tone burst 500 Hz used (Bio Logic Natus 102 System Corp Navigator Pro BERA device). We recorded the absolute latency of waves I, III, and V, and the interpeak latency of waves I-III, III-V, and I-V. Wave prolongation was included if the absolute latency of waves I, III, V exceeded 1.8 m/s, 3.9 m/s, and 5.8 m/s, and if the interpeak latency 1-III, III-V, I-V if exceeded 2.2 m/s, 2.2 m/s, and 4.4 m/s.[11] ABR electrode placement was consistent across all patients. Hyperacusis was diagnosed using the M-CHAT-R questionnaire.[12] Lastly, the severity of ASD was assessed using the Childhood Autism Rating Scale (CARS) instrument.[z]

Descriptive findings were tabulated and presented in frequencies and proportions for categorical variables, and in mean ± standard deviation (SD) or median and interquartile ranges (IQR) for continuous variables, depending on the result of normality distribution tests with Shapiro-Wilk test, acknowledging the small number of subjects recruited in this study (n<50). The association between hyperacusis with ABR findings and CARS score were tested using independent sample T-tests or Mann-Whitney U tests, while the correlation between CARS and ABR findings were analysed using Pearson or Spearmen tests, whichever appropriate. These statistical tests were chosen due to their suitability for comparing means between groups and assessing correlations based on the data distribution and measurement scale. All analyses were performed using the Statistical Package for Social Science 27.0 (SPSS Inc., Chicago, IL), and a two-sided p-value of <0.05 were deemed statistically significant.

RESULTS

A total of 26 normal-hearing children with ASD (52 ears) were included for analysis. Twenty-two of them were boys (88.5%), and a majority were aged between three and five years old (61.5%) with median (5.00 [4.75-6.25]). CARS in children were categorize into mild- moderate (10 [38.5%]) and severe (16 [61.5%]) with median of (40.00 [35.00 - 43.00]). About 69.2% children had reported symptoms pertaining to hyperacusis (Table I). ABR findings revealed that a majority of the study population had a prolonged latency of interpeak wave I-III (46 ears, 88.5%), followed by wave III (22 ears, 42.3%), wave V (11 ears, 21.6%), and interpeak wave I-V (8 ears, 15.4%). On the other hand, prolonged latency in wave I and interpeak wave I-III were observed in only one (1.9%) and three ears (5.8%), respectively (Table II).

Correlation between ABR findings, hyperacusis and the severity of ASD

No statistically significant correlation was found between ABR wave latencies and the severity of ASD, as tested using CARS (Table III). However, we found a slight, marginally significant correlation between wave III latency in the left ear and CARS score (r=0.359, p=0.072). Similarly, the severity of ASD was also not associated with the occurrence of hyperacusis (median CARS score: 39.5 [IQR 35.0-43.0] vs. 40.5 [35.5-43.0], p=0.737. (Figure 1) The box plot shows the distribution of CARS scores in individuals with and without hyperacusis. There was no significant difference in median CARS score between the two group (p=0.737) (Figure 1).

Correlation between ABR findings and hyperacusis

We found that the absolute latency of wave V in both ears were shorter in children with hyperacusis (right ear: median 5.57 ms [IQR 5.39-5.72] vs 5.74 ms [IQR 5.65-6.03], p=0.042; left ear: 5.57 [5.42-5.72] vs 5.85 [5.67-6.14], p=0.005). Similarly, the latency of interpeak wave I-V were also shorter in children with hyperacusis (right ear: 4.16 ms [3.89-4.22] vs 4.25 [4.10-4.66], p=0.050; left ear: 4.08 ms [3.83-4.16] vs 4.40 [4.21-4.67], p=0.004). (Figure 2A, 2B) Meanwhile, the absolute latency of wave III was only significantly shorter in the right ear (3.80 ms [3.70-3.92] vs 3.93 ms [3.87-3.98], p=0.029), while the latency of interpeak wave III-V only in the left ear (1.73 ms [1.61-1.87] vs 1.90 ms [1.80-2.16], p=0.006). No significant correlation was found for other ABR waves (Figure 2A, 2B).

DISCUSSION

Auditory brainstem response (ABR) is an examination of the synchronization activity of the auditory nerve in response to acoustic stimuli. The electrical potentials from cranial nerve VIII and neurons along the brainstem are recorded with electrodes on the scalp in the form of electrophysiological waves.[14] There are three important waves in ABR: wave I, originating from the distal part of nerve VIII; wave III, from the cochlear nucleus; and wave V, from the lateral lemniscus and inferior colliculus.[15] Previous studies have shown that there were substantial changes in the superior olivary complex in children with ASD, suggesting that hypoplasia and dysmorphology occur throughout the auditory brainstem in the pathophysiologic process of ASD, thus resulting in abnormal wave latencies during ABR testing.[16] This is consistent with our findings where most abnormalities were observed in wave III and V, thus confirming that structural abnormalities in ASD children occurred in the central auditory system.

Table I: Subject characteristics

Characteristics	N	(%)
Age (years)		5.00 (4.75-6.25)
3-5	16	61.5%
6-8	10	38.5%
Sex		
Boys	23	88.5%
Girls	3	11.5%
Hyperacusis		
Yes	18	69.2%
No	8	30.8%
CARS		40.00 (35.00 - 43.00)
Mild- moderate	10	38.5%
Severe	16	61.5%

Data are presented in frequencies and proportions

Table II: Proportion of prolonged absolute latency among the study population as tested with auditory brainstem response click (N=52 ears)

		Right ear; n (%)		Left ear; n (%)		Total; n (%)	
		Prolonged	Normal	Prolonged	Normal	Prolonged	Normal
ABR wave	Wave I	0 (0%)	26 (100%)	1 (3.8%)	25 (96.2%)	1 (1.9%)	51 (98.1%)
	Wave III	11 (42.3%)	15 (57.7%)	11 (42.3%)	15 (57.7%)	22 (42.3%)	30 (57.7%)
	Wave V	4 (15.4%)	22 (84.6%)	7 (26.9%)	19 (73.1%)	11 (21.6%)	41 (78.4%)
	Int wave I-III	24 (92.3%)	2 (7.7%)	22 (84.6%)	4 (15.4%)	46 (88.5%)	6 (11.5%)
	Int wave III-V	2 (7.7%)	24 (92.3%)	1 (3.8%)	25 (96.2%)	3 (5.8%)	49 (94.2%)
	Int wave I-V	3 (11.5%)	23 (88.5%)	5 (19.2%)	21 (80.8%)	8 (15.4%)	44 (84.6%)

Table III. Correlation between auditory brainstem response wave latencies and the severity of autism spectrum disorders

	Latency	Correlation (r)	P-value
Right ear	Wave I	-0.212	0.299[b]
	Wave III	0.201	0.325[a]
	Wave V	0.065	0.752[b]
	Int wave I-III	0.088	0.667[a]
	Int wave III-V	-0.085	0.680[b]
	Int wave I-V	0.135	0.512[a]
Left ear	Wave I	-0.03	0.883[b]
	Wave III	0.359	0.072[a]
	Wave V	0.092	0.655[a]
	Int wave I-III	0.209	0.305[b]
	Int wave III-V	-0.179	0.382[a]
	Int wave I-V	0.120	0.561[b]

[a]Pearson correlation test; [b]Spearman Rank test

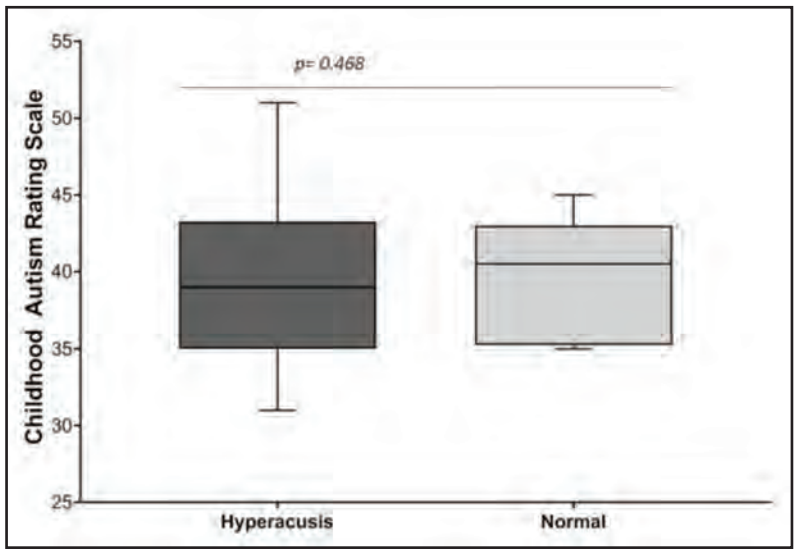

Fig. 1: Association between ASD severity and occurrence of hyperacusis

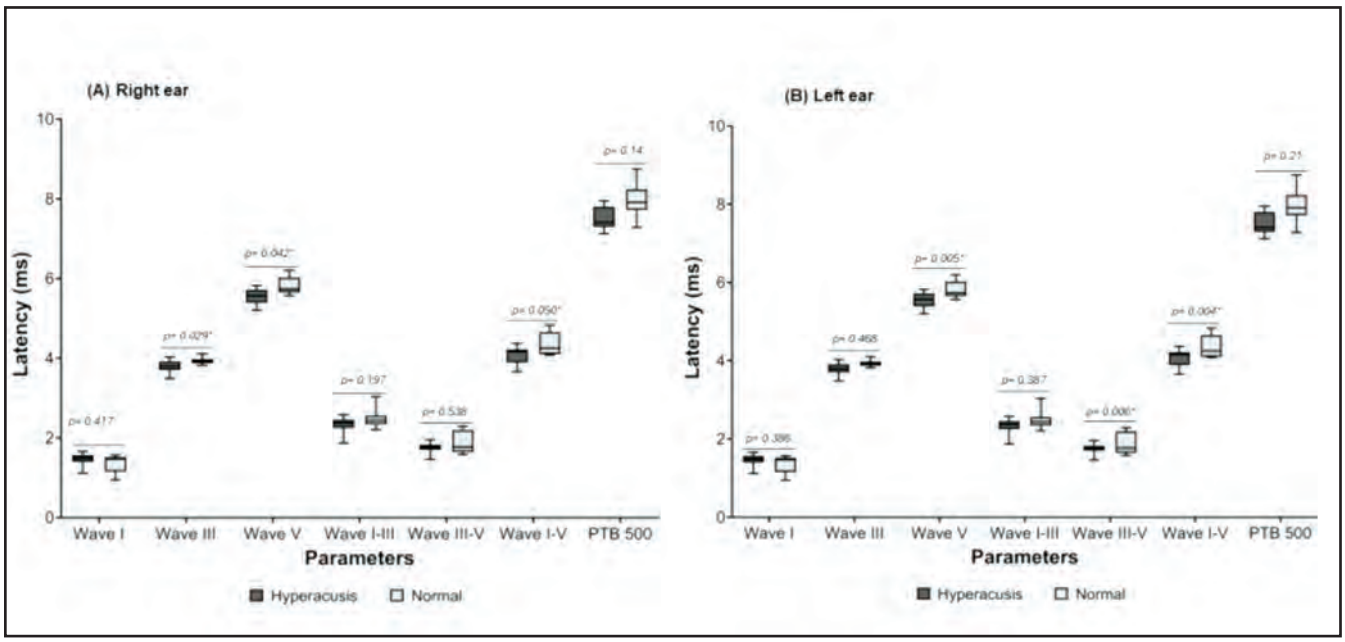

Fig. 2: Box plot illustrating ABR findings in individual with hyperacusis and normal hearing. Asterisk (*) denotes statistically significant difference between groups for specific ABR wave.

The ASD population is highly heterogeneous, leading to varied ABR responses. For example, a study by Madelyn Cate found that while some ASD children showed significantly longer latencies, others did not, suggesting that the differences may be more central in the auditory system rather than at the brainstem level. Additionally, ABR findings can vary based on the age and developmental stage of children, with younger children exhibiting different latencies. Sensory processing differences is a hallmark of ASD, it can also affect ABR results, as observed in Cate's study.[17]

The present study revealed that most ASD children had a prolonged latency in waves III and V, and in interpeak waves I-III, III-V, and I-V; with the prolongation of interpeak waves I-III observed in most cases. These finding are consistent with a meta-analysis by Talge et al., which demonstrated a link between ASD and prolonged latencies in wave III, V, and interpeak latencies I-III and I-V. 18 The speed of action potentials is primarily determined by the degree of myelination, path length, and axonal diameter but also can influenced by synchronization of neuronal signal release of changes in synaptic efficacy, as noted in studies by Distefano et al. and Waddington et al. Hypermyelination and hypomyelination of brainstem pathways is also frequently associated with ASD.[18–20]

These auditory brainstem abnormalities, particularly in the superior olivary complex, may contribute to delayed speech development, difficulty with sound localization, and altered sensory responses to auditory stimuli. These deficits can impair auditory processing and attention, which are clinically relevant in managing sensory challenges in ASD.[21,22] Furthermore, we also observed an asymmetrical prolongation of absolute wave latencies between the right and left ears, which might be explained by the fact that changes in cortical thickness asymmetry was found mostly in frontal, orbitofrontal, and temporal areas. The impact on ABR wave latency changes remain unconclusive and still needs further research to be understood.[23]

In addition to slower sound perception process, children with ASD are also vulnerable to sound hypersensitivity. These children typically frequently cover their ears when hearing exhausts, blenders, or certain phone rings that are usually perceived as normal sound stimuli in healthy children.[24,25] Our study proves the prevalent hyperacusis in children with ASD with more than two-thirds of the study population experiencing the symptoms. This is in line with the previous findings by Carson et al., who reported a prevalence of hyperacusis of 60.2% in children with ASD.[26] Nevertheless, further analysis revealed that the occurrence of hyperacusis was not correlated with the severity of ASD. While a plausible explanation for this phenomenon is yet to be fully known, it has been postulated that there is an extreme variability in hyperacusis with different individual ASD cases.[7] In addition, the severity of hyperacusis, which was not sought in the present study, may also contribute to the observed findings, especially considering in previous study most ASD children mild hyperacusis.[2]

To this date, the mechanism of hypersensitivity and hyposensitivity to auditory stimulus in children with ASD remain unclear. Imaging studies have identified weakened noise control that disrupts verbal message processing from the cochlear nucleus to the inferior colliculus and cortex.[27] There are several possible mechanisms leading to sound hypersensitivity. First, the medial olivary system in the superior olivary complex, which plays an essential part in filtering background noise in noisy environments and modulate cochlear function to prevent cochlear damage due to loud sounds, is found to be dysmorphic in children with ASD.16 In addition, in ASD children, auditory stimuli from

the lateral lemniscus are directly propagated to amygdala and the limbic system without passing through the geniculate body, thus resulting in excessive emotional responses upon hearing certain sounds.[27]

In the present study, we did not observe any correlation between ABR wave latencies and ASD severity. Our findings conform to a previous report by Samy et al., who also found no significant correlation between the absolute latency and interpeak latency of ABR click with CARS.[10] However, different findings was reported by Liu et al., who demonstrated a significant association between CARS and the wave III latency on the right ear (r=0.693), and interpeak latency I-III on the right (r=0.62) and left ear (r=0.594).[28] These suggest that the correlation between ABR wave latencies and CARS score remain equivocal, thus warranting further investigation as the underlying mechanism leading to these conflicting findings remain unknown. However, it should be noted that ABR wave latencies are likely to be influenced by stimulation frequency and repetition, and thus ABR patterns in children with ASD may vary widely.[28]

On the other hand, the present study indicates that ABR wave latencies may be correlated with hyperacusis, especially in wave V and I-V. This has been previously demonstrated by Refat et al., which showed that the absolute latency of wave III and V were shorter in children with hyperacusis.[29] Additionally, this correlation was observed in an exposure-gradient relationship where absolute wave III and V latencies shortened with increasing duration of hyperacusis. This might be explained by the possibility of specific over-activation of the medial olivocochlear system in the brainstem, and the type II cochlear afferents at the level of outer hair cells, thus resulting in a diminished baseline motile responses due to the activation of posteroventral cochlear nucleus neurons triggered.[29]

The present study presents with several limitations. First, the absence of healthy controls limited the interpretability of our findings. In particular, we were unable to investigate the correlation of ABR wave latencies with the occurrence of ASD, and the association between ABR wave latencies and ASD severity with a broader spectrum of hyperacusis severity. In addition, the cross-sectional design limited our ability to investigate the long-term trends of ABR findings and the progression of ASD and hyperacusis over time. To our knowledge, this is one of the very few studies investigating the association between ABR wave latencies, hyperacusis, and ASD severity. Further large-scale studies investigating ASD children with a broader spectrum of severity of ASD and hyperacusis are required to corroborate our findings.

CONCLUSION

There was no significant correlation between the absolute latency of ABR waves, hyperacusis, and ASD severity in young children with normal hearing. However, there was prolonged absolute and interpeak latencies, particularly in waves I-III, III, and V. Interestingly, ABR latencies were generally shorter in children with hyperacusis, likely reflecting its underlying pathophysiology. ABR wave latency could be a useful tool for early ASD screening, enabling timely intervention and therapy, which can help improve outcomes by reducing morbidity and enhancing the quality of life for patients.

ACKNOWLEDGEMENT

None

FUNDING

None

CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Baumer N, Spence SJ. Evaluation and Management of the Child With Autism Spectrum Disorder. Contin Lifelong Learn Neurol 2018; 24(1): 248–75.
2. Maenner MJ, Warren Z, Williams AR, Amoakohene E. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. 2024; 72(2).
3. Windiani IGT, Soetjiningsih S, Sugitha AGA, Lestari KA. Indonesian Modified Checklist for Autism in Toddler, Revised with Follow-Up (M-CHAT-R/F) for Autism Screening in Children at Sanglah General Hospital, Bali-Indonesia. Indones Modif Checkl Autism Toddler, Revis with Follow Autism Screen Child Sanglah Gen Hosp Bali-Indonesia. 2016; 5(2).
4. McKenna K, Prasad S, Cooper J, King AM, Shahzeidi S, Mittal J, et al. Incidence of Otolaryngological Manifestations in Individuals with Autism Spectrum Disorder: A Special Focus on Auditory Disorders. Audiol Res 2024 4; 14(1): 35–61.
5. Rinaldi LJ, Simner J, Koursarou S, Ward J. Autistic traits, emotion regulation, and sensory sensitivities in children and adults with Misophonia. J Autism Dev Disord 2023; 53(3): 1162–74.
6. Zwaigenbaum L, Penner M. Autism spectrum disorder: advances in diagnosis and evaluation. BMJ 2018; k1674.
7. Danesh AA, Howery S, Aazh H, Kaf W, Eshraghi AA. Hyperacusis in Autism Spectrum Disorders. Audiol Res 2021; 11(4): 547–56.
8. Martin A, Bloch MH, Volkmar FR. Autism Spectrum Disorder. In: Lewis's Child And Adolescent Psychiatry. 5th ed. 2018. p. 1164–86.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. 2013. 50 p.
10. Samy KL, Osman DM, Selim MH, Mohamed RA. Communication skills, sensory integration functions, and auditory brainstem response: findings in a group of Egyptian children with autistic features. Egypt J Otolaryngol 2012; 28(2): 117–26.
11. Prendergast G, Tu W, Guest H, Millman RE, Kluk K, Couth S, et al. Supra-threshold auditory brainstem response amplitudes in humans: Test-retest reliability, electrode montage and noise exposure. Hear Res 2018; 364: 38–47.
12. Soetjiningsih, Windiani IGAT, Adnyana IGANS. Pedoman Pelatihan- Deteksi Dini dan Diagnosis Gangguan Spektrum Autisme (GSA). UKK Tumbuh Kembang-Pediatri Sosial Bagian/SMF Ilmu Kesehatan Anak FK UNUD-Sanglah, editor. Denpasar; 2015. 60 p.
13. Moon SJ, Hwang JS, Shin AL, Kim JY, Bae SM, Sheehy-Knight J, et al. Accuracy of the Childhood Autism Rating Scale: a systematic review and meta-analysis. Dev Med Child Neurol 2019; 61(9): 1030–8.
14. Picton TW. Auditory brainstem responses: peaks along the way. In: Human auditory evoked potentials. 2011. p. 215.

15. Källstrand J, Niklasson K, Lindvall M, Claesdotter-Knutsson E. Reduced thalamic activity in ADHD under ABR forward masking conditions. Appl Neuropsychol Child 2022;16:1–7.
16. Mansour Y, Kulesza R. Three dimensional reconstructions of the superior olivary complex from children with autism spectrum disorder. Hear Res 2020;393:107974.
17. Cate M. Auditory Brainstem Response in Autistic Children: Potential Implications for Sensory Processing. Brigham Young University; 2022.
18. Talge NM, Tudor BM, Kileny PR. Click-evoked auditory brainstem responses and autism spectrum disorder: A meta-analytic review. Autism Res 2018;11(6):916–27.
19. Gonçalves AM, Monteiro P. Autism Spectrum Disorder and auditory sensory alterations: a systematic review on the integrity of cognitive and neuronal functions related to auditory processing. J Neural Transm 2023; 14;130(3):325–408.
20. Hanaie R, Mohri I, Kagitani-Shimono K, Tachibana M, Matsuzaki J, Hirata I, et al. White matter volume in the brainstem and inferior parietal lobule is related to motor performance in children with autism spectrum disorder: A voxel-based morphometry study. Autism Res 2016;9(9):981–92.
21. Kabil SE, Abdelshafy R, Ahmed AIA, Zahran AM, Attalah M, Sallam Y, et al. Mismatch Negativity and Auditory Brain Stem Response in Children with Autism Spectrum Disorders and Language Disorders. J Multidiscip Healthc 2023;16:811–7.
22. Miron O, Ari-Even Roth D, Gabis L V., Henkin Y, Shefer S, Dinstein I, et al. Prolonged auditory brainstem responses in infants with autism. Autism Res 2016;9(6):689–95.
23. Postema MC, van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, et al. Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets. Nat Commun 2019;10(1):4958.
24. Gravel JS, Dunn M, Lee WW, Ellis MA. Peripheral Audition of Children on the Autistic Spectrum. Ear Hear 2006;27(3):299–312.
25. Gomes E, Pedroso FS, Wagner MB. Hipersensibilidade auditiva no transtorno do espectro autístico. Pró-Fono Rev Atualização Científica 2008;20(4):279–84.
26. Carson TB, Valente MJ, Wilkes BJ, Richard L. Brief Report: Prevalence and Severity of Auditory Sensory Over-Responsivity in Autism as Reported by Parents and Caregivers. J Autism Dev Disord 2022; 10;52(3):1395–402.
27. Stefanelli ACGF, Zanchetta S, Furtado EF. Hiper-responsividade auditiva no transtorno do espectro autista, terminologias e mecanismos fisiológicos envolvidos: revisão sistemática. CoDAS 2020;32(3).
28. Liu Y, Liu Z, Diao T, Song P, Hu Q, Jiang N. Exploring the Relationship Between Auditory Brainstem Response Testing and Disease Progression in Pediatric Autism Spectrum Disorder. Altern Ther Health Med 2024;30(3):51–5.
29. Refat F, Wertz J, Hinrichs P, Klose U, Samy H, Abdelkader RM, et al. Co-occurrence of Hyperacusis Accelerates With Tinnitus Burden Over Time and Requires Medical Care. Front Neurol 2021;18;12.

Pre-operative carcino-embryonic antigen prognosticates early disease-free survival following curative surgery for non-small cell lung cancer

Anand Sachithanandan, FRCSI(C-Th)[1,2], Azliana Abu Bakar Sajak, MSc[3], Hoh Hong Huat, PhD[3]

[1]Division of Cardiothoracic Surgery, Sunway Medical Centre, Sunway City, Selangor, Malaysia, [2]School of Medical & Life Sciences, Sunway University 3Sunway Clinical Research Centre, Sunway Medical Centre, Sunway City, Selangor, Malaysia

ABSTRACT

Introduction: Serum carcinoembryonic antigen (CEA) is prognostic for recurrence and survival in treated NSCLC. This prospective observational study evaluated CEA as a prognostic or surveillance biomarker in resectable early NSCLC.

Materials and Methods: 18 patients with histologically confirmed early NSCLC (stage I-IIIA) were recruited from October 2019 to January 2021. The serum CEA was measured pre-operatively, and then at 6, 12, 18 and 24 months post-operatively, in conjunction with routine CT and/or CT-PET surveillance scans.

Results: All patients had a curative R0 anatomical resection (lobectomy) with concurrent systematic mediastinal nodal dissection via a uniportal minimally invasive approach under single lung ventilation general anaesthesia. There was no operative, in-hospital or 30-day mortality. 7 patients (39%) had an elevated pre-operative baseline CEA level > 5.0ng/ml. The mean number of nodes sampled intra-operatively was 15.

At median follow-up of 42 months, 11/18 (61.1%) patients were recurrence-free. There were no deaths and two recurrences (18.2%) amongst patients with a CEA < 5 (n=11). In the CEA > 5 subgroup (n=7), there were two deaths (28.5%) and 5/7 (71.4%) patients had a radiological recurrence. There was no difference in overall survival however disease-free survival (DFS) was significantly inferior in patients with a baseline CEA > 5. Median DFS was not reached in patients with CEA < 5 and 18 months in those with an elevated CEA > 5 (p<0.001)

Conclusion: Almost 40% of local NSCLC patients had an elevated baseline CEA suggesting this is a useful prognostic and surveillance biomarker to incorporate in the routine work-up for any newly diagnosed NSCLC. Despite curative R0 resection and extensive intra-operative mediastinal lymph node sampling, an elevated pre-operative CEA was associated with a significantly reduced DFS and may be a surrogate for more aggressive tumour biology. Such patients will benefit from meticulous post resection surveillance and adjuvant therapy beyond conventional TNM criteria.

KEYWORDS:
Carcinoembryonic antigen, non small cell lung cancer, disease-free survival

INTRODUCTION

Lung cancer is a common cancer and leading cause of cancer-related mortality globally with approximately two million new cases and 1.8 million deaths annually.[1] Almost sixty percent of all new cases and mortalities occur in Asia. In Malaysia, it is the second most prevalent male cancer and most common cause of cancer-related mortality in men. In women, lung cancer is the third most prevalent malignancy but only breast cancer is more fatal. The generally poor outcomes observed here are due to a preponderance of advanced stage clinical presentation and late diagnosis in a majority of patients. Surgery as part of multi-modal therapy remains the standard of care for resectable non-small cell lung cancer (NSCLC) in medically fit patients, and offers the best chance of a cure, and long-term disease-free survival (DFS).

However, a considerable number of patients will experience a recurrence or metastasis after curative surgery. Stage-dependent local or distant relapse due to occult micrometastatic disease is seen in up to 45-75% of cases despite curative surgery with multi-modal treatment.[2-4] Timely detection of post-operative recurrence or metastasis facilitates swift intervention, which manifests with better survival. Early identification of patients with a worse prognosis due to subclinical occult disease and early detection of disease recurrence facilitates better disease control through more meticulous invasive pre-operative staging, diligent post resection surveillance and escalation of appropriate adjuvant therapies, respectively.

The National Academy of Clinical Biochemistry (NACB) has recommended a panel of serum tumour markers, including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA -21), neuron specific enolase (NSE), squamous cell carcinoma antigen (SCC), and progastrin-releasing peptide (ProGRP) to be incorporated as a complementary diagnostic, screening, prognostic and monitoring tool for lung cancer patients.[5] In particular, CEA, a naturally occurring glycoprotein, is a simple, inexpensive and widely available blood biomarker that has been shown to help prognosticate,

This article was accepted: 16 September 2024
Corresponding Author: Anand Sachithanandan
Email: anandsachithanandan@yahoo.com

monitor, and detect recurrent disease in advanced stages of adenocarcinoma subtype of NSCLC.[6-8] In the present study, we aimed to study the role of CEA as a prognostic or disease monitoring biomarker in resectable early-stage NSCLC patients.

MATERIALS AND METHODS

Study Design and Study Population

This was a prospective observational study of patients with resectable early-stage NSCLC. Ethical approval was obtained from Sunway Medical Centre's Independent Research Ethics Committee (Reference number: 011/2018/IND/FR). Additionally, written informed consent was obtained from all participants prior to enrolment. Eighteen patients with histologically confirmed early NSCLC (clinical Stage I-IIB) were recruited between October 2019 and January 2021 at Sunway Medical Centre. All patients were clinically staged pre-operatively with a PET-CT scan and if indicated, a contrasted MRI brain scan.

Surgical Procedure

All operations were performed by a single UK board-certified cardiothoracic surgeon under general anaesthesia with a double lumen endobronchial tube to achieve single lung ventilation. The standard operation in all patients was a curative anatomical lobectomy with concurrent systematic mediastinal lymph node dissection, performed with a minimally invasive uniportal approach.

Data Collection, CEA and Radiographic Image Analysis

Demographic and clinical data of the patients, including age, ethnicity, smoking status, and TNM (Tumour, Node, Metastasis) staging, as well as histological type, were retrieved from medical records. Blood samples were collected pre-operatively and at 6, 12, 18, and 24-months post-operation. The blood samples were processed within an hour of collection to obtain the serum before being subjected to a commercial electrochemiluminescent assay measuring the levels of CEA, CYFRA-21, ProGRP, SCC, and NSE. The serum concentrations of the tumour biomarkers were analyzed using the Cobas® e 411 analyzer (Roche Diagnostics, Mannheim, Germany). The normal CEA reference level used by the hospital laboratory was between 0-5 ng/ml. The biomarker analyses were conducted in tandem with routine surveillance CT and/or PET-CT scans.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 29.0 software. Descriptive statistics were used for demographic data. Continuous variables were presented as mean, median (IQR), while categorical data were presented in frequency or percentage. The cumulative recurrence and survival rates were calculated using the Kaplan-Meier method and differences between the groups were assessed by the log-rank test. For this study, the overall survival (OS) was defined as the time from surgery to death from any cause, and disease-free survival (DFS) was defined as the interval from surgery to the first documented suspected radiological recurrence on CT and/or PET-CT imaging. A p-value <0.05 was considered as statistically significant.

RESULTS

The mean patient age was 63.8 years, ranging from 52 to 79 years old, with a majority of Chinese ethnicity, with all but one having an adenocarcinoma histology. There was no operative, in-hospital or 30-day mortality. All patients had a complete R0 tumour resection with pathologically confirmed clear microscopic margins and the mean number of ipsilateral mediastinal (N1/N2) lymph nodes sampled intra-operatively was 16. Notably, one patient received neoadjuvant therapy with an oral tyrosine kinase inhibitor, osimertinib, to downstage the tumour from Stage IIA to IA. Five patients whose tumours harboured an Epidermal Growth Factor Receptor (EGFR) mutation were treated with adjuvant platinum-based chemotherapy and osimertinib. Patient demographics, disease stage, operative data, and tumour biology are summarized in Tables I-III.

In total, 7/18 (38.9%) patients had an elevated pre-operative baseline CEA level (i.e., > 5.0 ng/ml), two of whom were active smokers. Three patients (42.9%) with elevated baseline CEA levels had normalized serum CEA concentrations (< 5.0 ng/ml) at 6-months follow-up, post-surgery. Survival was determined by a telephonic survey or where not contactable, date of the last outpatient clinic review. At a median follow-up of 42 months, 11 of the 18 patients (61.1%) were recurrence-free. There were no deaths and two recurrences (18.2%) amongst patients with a baseline CEA < 5 (n=11). In the baseline CEA >5 subgroup (n=7), there were two mortalities (28.6%) and 5 of the 7 (71.4%) patients had a documented radiological recurrence. There was no significant difference in early survival in both groups (p= 0.06) (Figure 1). However, patients with a baseline CEA > 5 had a significantly inferior DFS. The median DFS was not reached in patients with a baseline CEA < 5 and 18 months in patients with a baseline CEA> 5 (p< 0.01) (Figure 2).

In patients with an elevated baseline CEA, serial post-operative measurements offered good potential for detection of early relapse, facilitating swift intervention as illustrated by two specific cases: In one patient (left upper lobectomy for cT1b N0 (stage 1A2) disease), the CEA normalized at 6-months post-surgery (from a baseline 6.0 ng/ml to 3.5 ng/ml) then a subsequent mild rise (CEA 6.3 ng/ml) concurred with a new sub-centimetre fluorodeoxyglucose (FDG)-avid (SUV 4.05) left paravertebral T2 level mediastinal nodule, treated empirically with stereotactic ablative radiotherapy for a presumed metastasis as the small size and deep location precluded safe biopsy.

In another case (pT1cN0 stage 1A3, elevated baseline CEA (13.4 ng/ml), the biomarker outperformed routine imaging, detecting a suspected recurrence six months prior to any radiologically visible disease. At 12 months post-surgery, the CEA rose to 17.3 ng/ml with no visible disease on PET-CT imaging and the patient remained well. A further six months later, at 18 months post-surgery, the elevated CEA (99.0 ng/ml) correlated with two tiny FDG-avid ipsilateral pleural nodules and uptake at L5/S1 vertebrae suggestive of recurrence. The patient died 23 months post-surgery from disease progression despite chemoradiotherapy. This was one of two recorded mortalities in our series at follow-up at 3 years, both in patients with elevated baseline CEA levels. In this case, there was no apparent pathological nodal

Table I: Summary of patient demographics, operative information, clinical and pathological characteristics

	n (%)
Total	18
Gender	
Female	10 (55.6)
Male	8 (44.4)
Ethicity	
Chinese	16 (88.8)
Indian	1 (5.6)
Others	1 (5.6)
Smoking Status	
Active smoker	4 (22.2)
Ex-smoker	2 (11.1)
Non-smoker	12 (66.7)
Pathological Stage	
IA	12 (66.7)
IB	1 (5.6)
IIA	1 (5.6)
IIB	3 (16.7)
IIIA	1 (5.6)
Operation Site	
Right Upper Lobe	3 (16.7)
Right Middle Lobe	4 (22.2)
Right Lower Lobe	4 (22.2)
Left Upper Lobe	7 (38.9)
Lymph Nodes Involvement	
Yes	3 (16.7)
No	15 (83.3)
Tumour Histology	
Adenocarcinoma	17 (94.4)
Squamous	1 (5.6)
Histology Subtypes for Adenocarcinoma	
Acinar	16 (94.1)
Not Otherwise Specified (NOS)	1 (5.9)
Tumour Differentiation	
Well	6 (33.3)
Moderate	10 (55.6)
Poor	2 (11.1)
Histologic Descriptor	
Visceral Pleural Invasion (VPI)	3 (16.7)
Lymphovascular Invasion (LVI)	1 (5.6)
Spread Through Air Spaces (STAS)	3 (16.7)
Neoadjuvant Therapy	
Yes	1 (5.6)
No	17 (94.4)
Adjuvant Therapy	
Yes	5 (27.8)
No	13 (72.2)
Baseline CEA	
Low (< 5.0 ng/ml)	11 (61.1)
High (> 5.0 ng/ml)	7 (38.9)

upstaging as the 26 mediastinal nodes sampled at surgery were histologically negative, excluding occult nodal disease.

DISCUSSION

CEA is a non-specific biomarker traditionally utilized for detection and surveillance of colorectal and liver cancer. Additionally, it is the most widely used tumour marker in patients with NSCLC but may be elevated in smokers without malignancy, with advancing age and in some benign lung conditions. The reported cut-off value for a diagnostic CEA range from 2.5-10.0 ng/ml. This variation is due to the different measurement techniques employed such as enzyme immunoassay and radioimmunoassay. In any patient with an elevated CEA, it is imperative that gut and lung pathologies are excluded with endoscopy and appropriate thoracic imaging, respectively. CEA may have a useful role for risk stratification, surveillance and prognostication of some patients with suspected or confirmed NSCLC. A recent meta-analysis (12 studies; 4666 patients) revealed that a higher baseline pre-operative CEA level was associated with a higher mortality and more lymph node involvement in patients with early NSCLC (clinical stage I disease).[9] Patients with elevated baseline CEA levels may be clinically understaged as occult disease may be underestimated by imaging alone. Hence a lower threshold for invasive mediastinal lymph node staging and even a contrasted MRI brain scan should be considered in such individuals. Other

Table II: Patient Demographics, Operative Information and Clinical Characteristics

Patient	Age	Gender	Ethnicity	Smoking Status	Clinical Stage	Pathological Stage	Operation site	Number of LN Sampled	Number of LN Involved	Baseline CEA Level	Neoadjuvant Therapy	Adjuvant Therapy	Mutation	DFS[a] (Months)	Overall Survival (Months)
1	79	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RML	11	0	3.2	No	No	No	52	52
2	60	F	C	Non-smoker	T1b N0 (IA2)	T1c N0 (IA3)	RML	6	0	1.3	No	No	EGFR	50	50
3	59	F	C	Non-smoker	T1c N1 (IIB)	T2a N1 (IIB)	RLL	15	1	15.2	No	Yes	EGFR	49	49
4	58	M	C	Active smoker	T2a N0 (IB)	T1c N0 (IA3)	RLL	9	0	3.1	No	No	EGFR	10b	49
5	73	M	I	Non-smoker	T1b N0 (IA2)	T1b N0 (IA2)	LUL	23	0	6	No	No	EGFR	10b	48
6	63	M	C	Non-smoker	T1c N0 (IA3)	T1b N0 (IA2)	LUL	18	0	3	No	No	No	48	48
7	62	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	LUL	14	0	3.6	No	No	No	47	47
8	62	M	C	Active smoker	T1b N0 (IA2)	T1b N0 (IA2)	RML	5	0	2.3	No	No	ALK	42	42
9	73	M	C	Ex-smoker	T2b N0 (IIA)	T2b N0 (IIA)	RUL	18	0	14.8	No	Yes	EGFR	42[b]	42
10	72	M	C	Ex-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RLL	20	0	1.7	No	No	EGFR	42	42
11	55	M	C	Active smoker	T2b N0 (IIA)	T2a N0 (IB)	LUL	34	0	55.9	No	No	No	13[b]	40
12	70	M	C	Active smoker	T3 N0 (IIB)	T3 N0 (IIB)	RUL	24	0	15.5	No	No	No	4c	4[c]
13	52	F	Others	Non-smoker	T1b N0 (IA2)	T1b N2 (IIIA)	LUL	5	2	4.9	No	Yes	EGFR	39	40
14	68	F	C	Non-smoker	T1c N0 (IA3)	T1c N1 (IIB)	RLL	28	3	2.2	No	Yes	EGFR	39	39
15	68	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	RML	26	0	13.4	No	No	No	18[b]	23[c]
16	61	F	C	Non-smoker	T2b N0 (IIA)	T1c N0 (IA3)	LUL	15	0	28.8	Yes	Yes	EGFR	14[b]	38
17	57	F	C	Non-smoker	T1b N0 (IA2)	T1b N0 (IA2)	RUL	8	0	1.7	No	No	EGFR	23[b]	37
18	59	F	C	Non-smoker	T1c N0 (IA3)	T1c N0 (IA3)	LUL	12	0	1.7	No	No	No	37	37

Abbreviations: F: Female; M: Male; C: Chinese; I: Indian; CEA: carcinoembryonic antigen; RML: Right middle lobectomy; RLL: Right lower lobectomy; RUL: Right upper lobectomy; LUL: Left upper lobectomy; LN: Lymph nodes; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; DFS: Disease Free Survival; OS: Overall survival

Notes:
[a] DFS was calculated from date of operation to last radiological recurrence date (for patients who relapsed) or last follow-up call date (for patients who are on remission) or death
[b] Relapse based on radiological report
[c] Died

Table III: Tumour Histopathology

Patient	Tumour Histology	Tumour Grade Differentiation	VPI	LVI	STAS	Margin
1	Adeno; Acinar	Moderate	No	No	No	Clear, R0
2	Adeno; Acinar	Moderate	No	No	Yes	Clear, R0
3	Adeno; Acinar	Well	No	No	Yes	Clear, R0
4	Adeno; Acinar	Moderate	No	No	Yes	Clear, R0
5	Adeno; Acinar	Moderate	No	No	No	Clear, R0
6	Adeno; Acinar	Moderate	No	No	No	Clear, R0
7	Adeno; Acinar	Well	No	No	No	Clear, R0
8	Adeno; Acinar	Moderate	No	No	No	Clear, R0
9	Adeno; NOS	Moderate	No	No	No	Clear, R0
10	Acinar; Acinar	Moderate	No	No	No	Clear, R0
11	Adeno; Acinar	Moderate	No	No	No	Clear, R0
12	Squamous	Poor	Yes	No	No	Clear, R0
13	Adeno; Acinar	Poor	No	No	No	Clear, R0
14	Adeno; Acinar	Moderate	No	No	No	Clear, R0
15	Adeno; Acinar	Well	Yes	Yes	No	Clear, R0
16	Adeno; Acinar	Well	Yes	No	No	Clear, R0
17	Adeno; Acinar	Well	No	No	No	Clear, R0
18	Adeno; Acinar	Well	No	No	No	Clear, R0

Abbreviations: Adeno: Adenocarcinoma; NOS: Not otherwise specified; VPI: Visceral pleural invasion; LVI: Lymphovascular invasion; STAS: Spread through air spaces; R0: No cancer cells seen microscopically at the primary tumour bronchial and lung resection margins

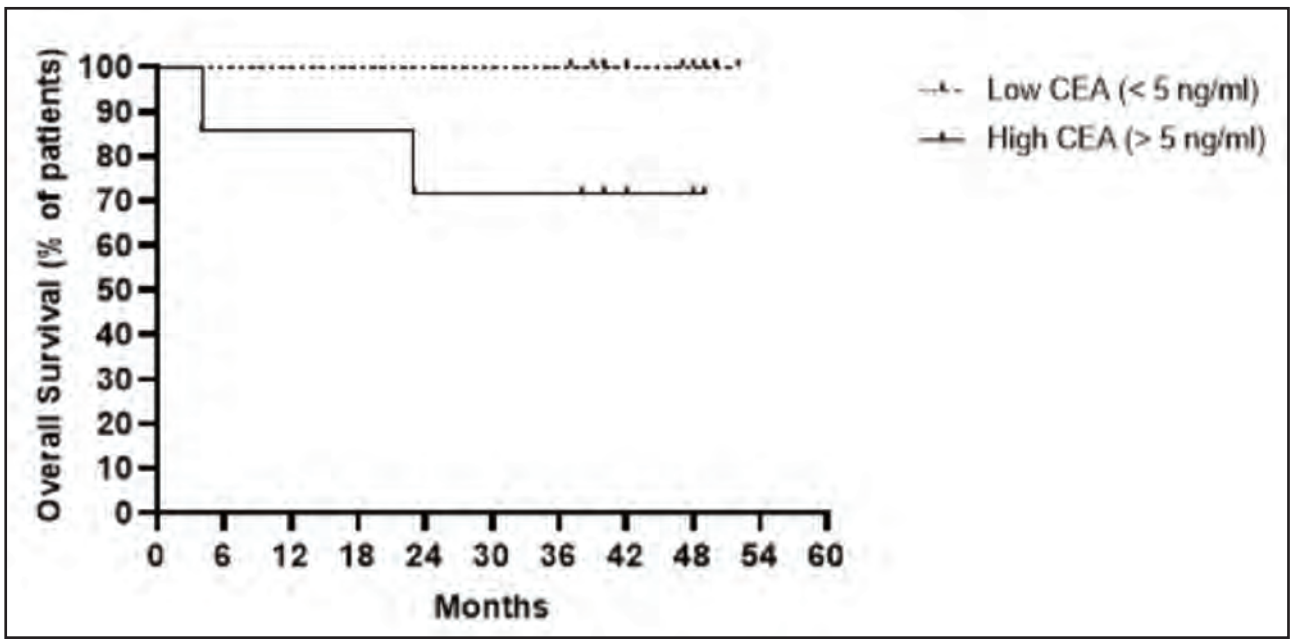

Fig. 1: Kaplan-Meier Curve for Overall Survival (OS). Symbols indicate censored observations where patients were last followed-up

studies have suggested that the post-operative CEA and post/pre-CEA ratio can be helpful to prognosticate patients.[10-12] Our study was hampered by sizeable follow-up data gaps as it was conducted during the COVID-19 pandemic hence we were unable to analyse the impact of post-operative CEA levels or the post/pre-CEA ratio. Patients however did attend for their follow-up visits and standard-of-care surveillance scans but just not at the designated time-points which resulted in several patients not being identified as study patients and appropriate blood samples not being taken. Hence, we were still able to accurately capture DFS based on radiological recurrence and ascertain their survival from their outpatient clinic visit/telephone call.

Risk Stratification

In our small study of 18 patients with histologically confirmed early NSCLC (clinical stage 1A2-IIB/ pathological stage 1A2-IIIA), almost 39% had an elevated baseline CEA suggesting this relatively inexpensive biomarker is worth incorporating to better refine lung cancer screening. In patients with a screening detected or incidental indeterminate pulmonary nodule (IPN), an elevated CEA raises clinical suspicion for a possible lung cancer. Due to low sensitivity and specificity, presently, serum CEA alone is not a discriminative enough biomarker for lung cancer screening. However, it may be a useful adjunct to existing criteria incorporating clinical risk profile and nodule

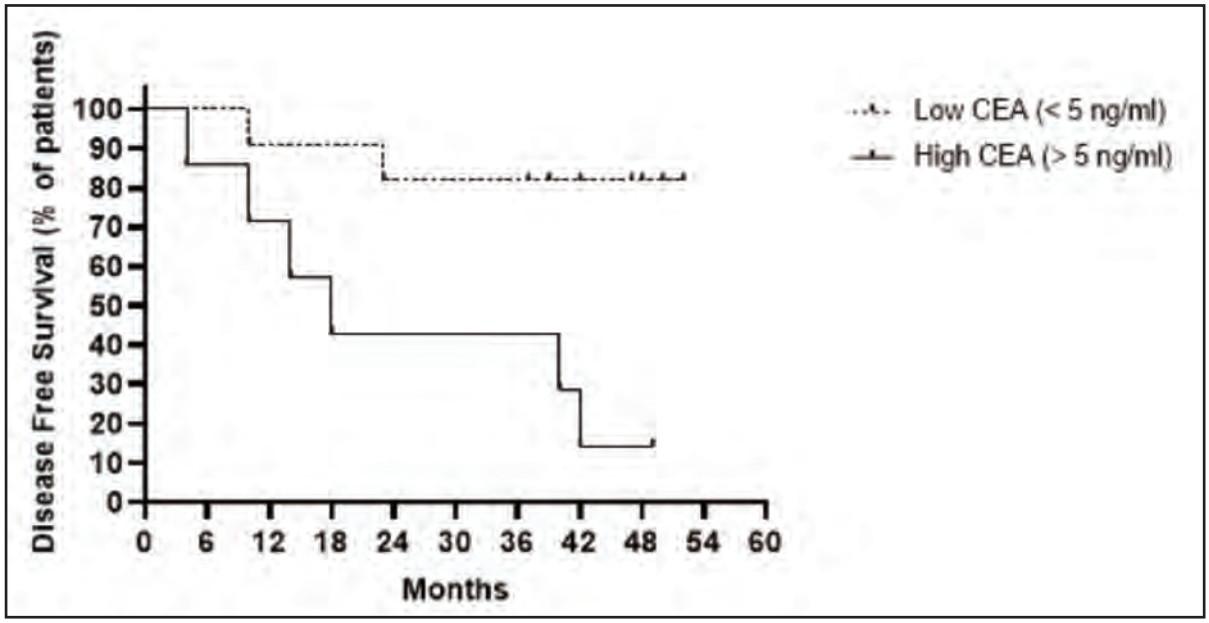

Fig. 2: Kaplan-Meier Curve for Disease Free Survival (DFS). Symbols indicate censored observations where patients were last followed-up

morphology and size, to better risk-stratify IPN patients both in terms of personalising surveillance CT screening intervals and to guide thresholds for histological tissue sampling. We intend to explore its potential use to augment artificial intelligence-enabled chest radiography (AI-CXR) screening as a prelude or triage to definitive low-dose computer tomography (LDCT) imaging. Broad lung screening with AI-CXR imaging has an IPN detection rate of approximately 2.35% in Malaysia though the incidence of an inherent NSCLC remains unknown.[13]

Surveillance

In patients with a confirmed NSCLC and an elevated baseline CEA, serial measurements at periodic intervals (e.g., 3 to 6 monthly) are helpful to monitor response to therapy including surgical resection, and for disease recurrence. The normalization of CEA levels we observed in three patients at 6 months post-surgery is well documented in the literature and a favourable prognostic factor.[9-11] A persistently high CEA level following resection suggests residual disease and may reflect more advanced occult disease from under-staging, sub-optimal resection or a surrogate for more aggressive tumour biology. However, the ability to detect low burden disease relapse or recurrence using pre- and post-operative CEA levels was most impressive as described in the two earlier cases. This offers an opportunity to not only personalize surveillance scan intervals by bringing forward a routine scheduled scan if clinical suspicion is high but also facilitates early intervention including escalation or commencement of adjuvant therapies, if indicated.

Prognosticate

Previous investigators have reported on the value of CEA to prognosticate outcomes and survival for treated early NSCLC.[8-12] An elevated baseline pre-operative CEA has been shown to correlate with an inferior DFS and overall survival. Furthermore, patients with a high pre-operative CEA that fails to normalize following surgery have a worse prognosis in terms of survival at 3 and 5 years.[3] This may be due to occult microscopic and subclinical nodal disease not apparent with conventional pre-operative PET-CT staging alone. A lower threshold for invasive mediastinal staging with endobronchial ultrasound (EBUS) or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), or mediastinoscopy may be warranted for such patients. Having said that, in the three patients we observed pathological nodal upstaging from extensive intra-operative mediastinal lymph node sampling to suggest subclinical occult nodal disease, only one had an elevated baseline CEA. With regards to outcomes, we observed significantly inferior DFS but not OS at 3 years for patients with an elevated baseline pre-operative CEA. The favourable overall survival and quality of life observed in these patients despite the poor DFS recorded could be a therapeutic reflection of adjuvant therapy or early empirical intervention. This highlights the value of timely detection and early intervention. However, as histological tissue confirmation was often not feasible or performed, it could also be attributed in part to 'overdiagnosis' and treatment of presumed radiological 'recurrences. It may also be a reflection of an underpowered study given the small sample size of patients with early-stage disease.

Nevertheless, an elevated baseline pre-operative CEA biomarker can serve as an additional prognosticator beyond conventional TNM staging to identify high-risk patients who may benefit from meticulous close surveillance and even adjuvant systemic therapies beyond traditional pathological staging criteria. Tumour biology in terms of histological grade and cell type, microscopic lymphovascular invasion or tumour spread through the air space are important features which elude current TNM staging criteria which emphasises tumour size and location, and nodal status. Emerging biomarkers like circulating tumour deoxyribonucleic acid (ctDNA) has promising potential to identify post resection

molecular residual disease and thus refine patient selection for appropriate escalation or de-escalation of adjuvant therapies but presently, their clinical use is limited by cost and availability. With growing use of pre-surgery down-staging neoadjuvant therapies like systemic chemo-immunotherapy and oral targeted therapies in selected patients with actionable genomic mutations, it will be interesting to observe the performance of CEA as an affordable biomarker to predict pathologic response and any corresponding survival benefit following surgery in patients with an elevated pre-therapy level.

LIMITATIONS AND FUTURE RECOMMENDATIONS

This was a small prospective observational single institution study with sizeable data gaps due to poor clinical follow-up, for the reasons previously outlined. A majority of patients were urban female non-smokers of Chinese ethnicity, predominantly with an adenocarcinoma histology. This patient demographic may reflect the case-mix at our institution as a tertiary private hospital in greater Kuala Lumpur. The suspected recurrences or relapse were largely clinical based on radio-metabolic findings, and not confirmed histologically. Our findings must be interpreted judiciously and not over-generalized to the wider heterogeneous population of Malaysian patients with NSCLC as the study may be underpowered due to the small sample size. Larger studies with longer follow-up are necessary to reaffirm the utility of CEA as a biomarker in the multi modal management of resectable early NSCLC.

CONCLUSION

Our study demonstrated that approximately 39% of patients with early resectable NSCLC of predominantly adenocarcinoma subtype had an elevated pre-operative baseline CEA. This suggests it would be helpful to incorporate a CEA blood test to the routine work-up of any newly diagnosed NSCLC patient. In patients with a confirmed NSCLC and elevated baseline pre-operative CEA, a normalization of serum biomarker level is expected post-surgery and is a favourable prognosticator. Serial measurement following resection in patients with an elevated baseline CEA can help monitor response to therapy and detect even low volume disease recurrence, possibly predating radiological findings. Baseline pre-operative serum CEA levels can prognosticate early DFS following curative surgery. The poor DFS observed in patients with an elevated baseline CEA may be due to occult subclinical nodal disease or a surrogate for more biologically aggressive disease. Such patients will benefit from meticulous biomarker and imaging surveillance, and appropriate adjuvant therapies beyond conventional TNM staging criteria.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Sunway Medical Centre for funding this study under the SunMed Research Fund. We also extend our sincere thanks to the Clinical Research Centre (CRC) staff, especially Dr. Chow Yock Ping, Ms. Loshini R. Moorthy, and Dr. Adrian Dass S. Muthudass, for their assistance with patient recruitment, data collection, and follow-up correspondence with the study patients.

REFERENCES

1. Global Cancer Facts & Figures, 5th Edition (2022). Atlanta: American Cancer Society, Inc 2024.
2. Al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. Eur J Cardiothorac Surg 1997; 12:380-4.
3. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet 2000; 355:479-85.
4. Carnio S, Novello S, Papotti M, Loiacono M, Scagliotti GV. Prognostic and predictive biomarkers in early stage non small-cell lung cancer: tumour based approaches including gene signatures. Transl Lung Cancer Res 2013; 2:372-81.
5. Stieber P, Hatz R, Holdenrieder S, Molina R, Nap M, Pawel JV et al. National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Lung Cancer. Tumor Biology 2006; 27.
6. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumour marker in lung cancer. Lung Cancer 2012; 76(2):138-43.
7. Molina R, Filella X, Auge JM, Fuentes R, Bover I, Rifa J et al. Tumor markers (CEA, CA 125, CYFRA 21-1, SCC and NSE) in patients with non-small cell lung cancer as an aid in histological diagnosis and prognosis. Comparison with the main clinical and pathological prognostic factors. Tumour Biol. 2003; 24:209-18.
8. Kao CH, Hsieh JF, Ho YJ, Ding HJ. Cytokeratin fragment 19 (CYFRA 21-1) and carcinoembryonic antigen for early prediction of recurrence of lung adenocarcinoma. Lung. 1999; 177:333-7.
9. Nasralla A, Lee J, Dang J, Turner S. Elevated preoperative CEA is associated with subclinical nodal involvement and worse survival in stage I non-small cell lung cancer: a systematic review and meta-analysis. J Cardiothorac Surg 2020;15: 318: 2-8.
10. Hsu WH, Huang CS, Hsu HS, Huang WJ, Lee HC, Huang BS et al. Preoperative serum carcinoembryonic antigen level is a prognostic factor in women with early non-small-cell lung cancer. Ann Thorac Surg 2007; 83(2):419-24.
11. Jiao Z, Cao S, Li J, Hu N, Gong Y, Wang L et al. Clinical associations of pre-operative and postoperative serum CEA and Lung Cancer Outcome. Front. Mol. Biosci. 2021; 8:686313.
12. Tomita M, Ayabe T, Chosa E, Nakamura K. Postoperative serum CEA level is a more significant prognostic factor than Post/Preoperative Serum CEA Ratio in Non-small Cell Cancer patients. Asian Pacific J Cancer Prevention 2015; 16: 7809-12.
13. Sachithanandan A, Lockman H, Azman RR, Tho LM, Ban EZ, Ramon V. The potential role of artificial intelligence-assisted chest X-ray imaging in detecting early-stage lung cancer in the community –a proposed algorithm for lung cancer screening in Malaysia. Med J Malaysia 2024; 79(1): 9-14.

ORIGINAL ARTICLE

Diagnostic Evaluation of Technetium-99 metastable TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography in the Differential Diagnosis of Parkinsonism in Hospital Kuala Lumpur: A preliminary experience

Kamalia Kamarulzaman, MMed (Nuc Med) (USM)[1], Nadiah Abd Razak, MMed (Nuc Med) (USM)[1], Ahmad Shahir Mawardi, MMed (Int Medicine) (UKM)[2], Siti Zarina Amir Hassan, MMed (Int Med) (UM)[1]

[1]Department of Nuclear Medicine Hospital Kuala Lumpur, [2]Department of Neurology Hospital Kuala Lumpur

ABSTRACT

Introduction: Parkinsonian syndrome encompasses a group of movement disorders characterized by symptoms such as tremor, rigidity, bradykinesia, and postural instability. While Idiopathic Parkinson's disease is the most common cause, several other etiologies can also result in parkinsonism. Identifying the specific type of Parkinsonian syndrome is essential due to its varying therapeutic and prognostic implications. This study aims to evaluate the role of Technetium-99 metastable TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography (Tc-99m TRODAT-1 SPECT-CT) in patients with parkinsonism.

Materials and Methods: The clinical data and scintigraphy findings of patients referred to the Department of Nuclear Medicine, Hospital Kuala Lumpur for Tc-99m TRODAT-1 SPECT-CT from July 2022 to July 2023 were retrospectively reviewed. Follow-up with primary team was conducted to determine the clinical implications and subsequent therapeutic management of the patients.

Results: Tc-99m TRODAT-1 SPECT-CT was performed on sixteen patients (10 females and 6 males) with a mean age of 55.2 years (range 26 to 75 years). Five patients exhibited normal scintigraphy findings, while eleven patients showed abnormal Tc-99m TRODAT-1 SPECT-CT results. The scintigraphy findings led to changes in therapeutic management for 81.3% of the patients. Additionally, 19% of the patients were referred for further evaluation with Fluorine-18 fluorodeoxyglucose PET to assist in diagnosing atypical Parkinsonian disease.

Conclusions: Tc-99m TRODAT-1 SPECT-CT is a readily available tool for assessing presynaptic dopamine transporters in patients with parkinsonism. This study demonstrated that Tc-99m TRODAT-1 SPECT-CT significantly impacts the diagnostic and therapeutic outcomes for patients with parkinsonism.

KEYWORDS:
Parkinsonian syndrome, parkinsonism, Parkinson's disease, Dopamine transporter, TRODAT

INTRODUCTION

Parkinsonian syndrome encompasses a variety of movement disorders characterized by symptoms such as tremors, rigidity, bradykinesia, and postural instability. The etiologies of parkinsonism can be broadly classified into neurodegenerative and non-neurodegenerative categories. Neurodegenerative causes, commonly linked to striatal dopaminergic deficiency, include Idiopathic Parkinson's Disease (IPD) and atypical Parkinson diseases such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia (LBD), and corticobasal degeneration (CBD).[1] In contrast, non-neurodegenerative causes include essential tremor (ET), drug-induced parkinsonism (resulting from dopamine receptor-blocking drugs or pallidal toxins), psychogenic or functional parkinsonism, vascular parkinsonism, adult-onset dystonic tremor, and normal pressure hydrocephalus.[1] The most prevalent cause of parkinsonism, IPD, is defined by the progressive loss of pre-synaptic dopaminergic neurons in the pars compacta of the substantia nigra.[2]

Among all the neurological diseases included in the Global Burden Disease, Injuries, and Risk Factors study, IPD has shown the fastest growth in prevalence, largely due to the aging population.[3] Statistically, Asia countries including Malaysia will gather more than 60% of the world's population age of at least 65 years old by the year 2030.[3] According to post-2000 records from the World Health Organization, the age-standardized incidence of IPD in the Western Pacific region, including Malaysia, ranges from 6.7 to 26.9 per 100,000 person-years.[3] Aging is associated with a decline in various components of the dopamine system, including dopamine-producing neurons in the substantia nigra, reduced D1/D2 receptor densities, and pre-synaptic DAT densities.[4] Studies indicate a nearly linear decline in striatal DAT binding by 46% between ages 18 and 88 years.[4] Conversely, Mozley et al. observed a nonlinear aging effect on DAT scans, with the most significant striatal loss occurring before age 40.[5]

Formerly, few studies have demonstrated approximately 75% of accuracy in diagnosing IPD clinically when compared to autopsy.[6] This accuracy may rise to 90% after evaluating

This article was accepted: 16 September 2024
Corresponding Author: Nadiah Abd Razak
Email: nadiah.abdrazak@yahoo.com

treatment response during follow-up.[7] Accurate diagnosis of various Parkinsonian syndromes is crucial due to differing treatment strategies and prognoses. This has increased the need for non-invasive diagnostic methods such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), or positron emission tomography (PET). Although MRI is useful for detecting anatomical and structural abnormalities, it has limited value in early-stage diagnosis as it does not reveal specific findings until the later stages of the disease.[8-10] This can delay diagnosis and treatment especially in cases of clinically uncertain parkinsonism. Studies have shown that 60% to 80% of presynaptic dopaminergic neurons are lost before parkinsonism symptoms manifest.[2,11] Therefore, SPECT and PET using various radiotracers offer early-stage recognition and diagnosis of parkinsonism.[12]

A systematic review found that DAT scans have 98% to 100% sensitivity and specificity in detecting nigrostriatal cell loss in IPD and clinically uncertain parkinsonism.[13] Kraemmer J et al. emphasized the validity of DAT imaging as a live marker of nigrostriatal dopaminergic degeneration, showing a high correlation between striatal DAT binding and post-mortem substantia nigra counts.[14] This is supported by numerous studies reporting a close relationship between DAT concentrations and striatal dopamine levels.[15]

Nuclear medicine imaging with SPECT and PET assesses the dopaminergic neurotransmitter system at both pre- and post-synaptic levels. Post-synaptic dopaminergic using SPECT or PET imaging can differentiate IPD from atypical Parkinson diseases.[1-2,16-21] While post-synaptic D2-receptor imaging with SPECT is not routinely performed due to limited radiotracer availability, F-18 fluorodeoxyglucose (FDG) PET imaging, which has higher diagnostic accuracy, has taken over this role.[22-25] Pre-synaptic dopaminergic imaging evaluates striatal dopaminergic deficiency in neurodegenerative diseases. The dopamine transporter (DAT) proteins that are accountable for the reuptake of dopamine are found at the pre-synaptic membrane of the dopaminergic neurons in the synaptic cleft. Several studies have described a close relationship between DAT concentrations and striatal dopamine levels.[26-28] Therefore, a DAT scan reflecting the degree of pre-synaptic dopaminergic neuron loss can serve as a diagnostic biomarker for parkinsonism.[1-2] Several tropane-based radiotracers like Iodine-123 FP-CIT (I123-ioflupane) and Technetium-99m TRODAT-1 (Tc-99m TRODAT-1) can assess DAT expression levels in the striatum using SPECT. Currently, no PET radiotracers for DAT imaging are commercially available.[1] Few studies have demonstrated that SPECT-based DAT imaging is a reliable alternative to PET for evaluating IPD patients.[29]

In clinical practice, IPD is distinguished from other parkinsonism causes using clinical features and assessment criteria, such as the Movement Disorder Society clinical diagnostic criteria for Parkinson's Disease (MDS-PD).[30] Tc-99m TRODAT-1 SPECT-CT imaging benefits IPD patients with atypical or vague parkinsonism findings that do not meet the typical IPD diagnostic criteria. It is also indicated for patients treated as IPD but showing unsatisfactory therapy response or for early-stage disease with mild parkinsonism.[31-32] Additionally, Tc-99m TRODAT-1 SPECT-CT can exclude non-neurodegenerative causes of parkinsonism, like ET or drug-induced parkinsonism, from neurodegenerative etiologies.

Qualitative visual interpretation of DAT SPECT images is performed in three orthogonal planes with trans-axial slices reformatted parallel to the line connecting the anterior and posterior commissures using the rainbow color scale. Various studies have shown that high accuracy in DAT SPECT interpretation can be achieved through visual interpretation by an experienced reader.[33] While qualitative visual interpretation is the primary approach, quantitative image analysis provides more objective readings. Studies have shown that adding quantitative assessment improves the diagnostic performance of Tc-99m TRODAT-1 SPECT-CT[17].

One advantage of using Tc-99m TRODAT-1 is its labelling with widely available sodium pertechnetate (Tc04-). It has rapid pharmacokinetics and is more cost-effective compared to cyclotron-produced I123-ioflupane.[20-21] Given the limited access to PET and increasing awareness of dopaminergic functional studies among clinicians, our center has decided to fully utilize our SPECT machine with Technetium-99m TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography (Tc-99m TRODAT-1 SPECT-CT). Our study, conducted at Hospital Kuala Lumpur, is the first dopaminergic scintigraphy study in Malaysia. We aim to share the clinical associations, practical aspects, and scintigraphy findings of Tc-99m TRODAT-1 SPECT-CT imaging as a diagnostic tool for parkinsonism and its clinical implications for patient management.

MATERIALS AND METHODS

Patient selection

This retrospective study, approved by the Malaysian Ministry of Health Medical Research Ethics Committee (MREC approval number: NMRR-20-1008-54807), adhered to the Declaration of Helsinki guidelines for human research. We analyzed clinical data and scintigraphy results from patients referred to the Department of Nuclear Medicine, Hospital Kuala Lumpur, for Tc-99m TRODAT-1 SPECT-CT scans from July 2022 to July 2023. Inclusion criteria encompassed patients exhibiting parkinsonism symptoms who successfully completed the Tc-99m TRODAT-1 SPECT-CT scan. Patients with MRI-confirmed vascular parkinsonism and those with poor image quality due to severe motion artifacts were excluded. Our records indicated 16 patients who underwent the Tc-99m TRODAT-1 SPECT-CT, all of whom were included in the study.

Patient preparation

Fasting was not required for the Tc-99m TRODAT-1 SPECT-CT. However, one patient with severe tremors received 2.5 mg intravenous Midazolam ten minutes before image acquisition to mitigate motion artifacts. Standard anti-Parkinsonian medications (L-DOPA, dopamine agonists, monoamine oxidase B inhibitors, N-methyl-D-aspartate receptor blockers, amantadine, and catechol-O-methyltransferase inhibitors) do not significantly affect DAT binding,[17] hence, these medications were not withheld. None of our patients were on drugs known to alter striatal DAT binding per European Association of Nuclear Medicine guidelines.[17]

Radiopharmaceutical
Tc-99m TRODAT-1 was prepared and quality-controlled using established methods. 5 mL of freshly eluted Tc04-containing 1480 MBq (max 1628 MBq) was added to a TRODAT-1 freeze-dried kit (GMS TRODAT-1 kit, Taiwan), shaken immediately, and heated in a tightly sealed heating block for 60 minutes at 121°C. Radiochemical purity was verified using instant Thin Layer Chromatography Paper method. [System 1: pre-cut Agilent iTLC SG 1.5 x 13 cm developed in NaCl 0.9% (O: 2 cm, SF: 12 cm, rf: 0); System 2: pre-cut Agilent iTLC SG 1.5 x 13 cm developed in acetone, dried, then developed in NaCl 0.9% (O: 2 cm, SF: 12 cm, rf: 1)]. The radiochemical purity of Tc-99m TRODAT-1 administered exceeded 90%, with a 4-hour post-reconstitution expiration time.

Image acquisition
Tc-99m TRODAT-1 SPECT-CT brain imaging was conducted four hours after intravenous injection of 740 MBq of Tc-99m TRODAT-1. Images were acquired using a dual-head parallel hole gamma camera with high-resolution low-energy collimators (Siemens Intervo Bold). Data were captured in a 128 x 128 matrix with 1.45 zoom through a 360° rotation (180° per head) in continuous mode (stop condition: Repeats/Phase: 10, Cycles/Repeat: 1, Time Per Cycle: 5 min, Number of Views: 64). Images were reconstructed using Filtered Back Projection with a ramp-Butterworth filter (cut-off: 0.40 cm, order: 10), and attenuation correction via CT was applied to better delineate anatomical structures. All patients' heads were secured to prevent motion artifacts.

Image analysis, data interpretation, and statistical analysis
Image processing was performed on a Siemens Intervo Bold workstation. Interpretation of striatal DAT binding involved both qualitative visual and quantitative analyses of the reconstructed Tc-99m TRODAT-1 SPECT-CT images. Qualitatively, normal basal ganglia showed good striatal-to-background ratio with symmetrical radiotracer uptake, while abnormal basal ganglia displayed reduced tracer uptake.[17]

Quantitative analysis used DAT Striatal analysis on Siemens Intervo Bold, employing a fully automated volume of interest (VOI) template to quantify distribution volume ratio (DVR) of the striatum, caudate, and putamen.[34] All regions were normalized to background activity from the occipital cortex. Boundaries of basal ganglia and occipital cortex were defined using brain CT on the automated template.[34]

Given the acquisition parameters' similarity, our quantitative analyses were compared with the age-specific normal database from Weng et al., who reported normal values as striatal binding ratio (SBR) rather than DVR.[35] Based on Fahmi et al., to utilise Weng et al. reference for normal value, each of patients' striatal subregion DVR value that was obtained from DAT Striatal analysis in Siemens Intervo Bold were minus with one (i.e., SBR= DVR-1).[34] However, for two patients (aged 26 and 37) no database comparison was available, as Weng et al.'s lower age limit was 50 years. Therefore, reporting for these patients was relied mainly on qualitative analysis.

The image analysis, data interpretation and statistical analysis were performed by an experienced nuclear neurology physician. Follow-up with primary teams determined clinical implications and subsequent patient management. Fisher's Exact Test examined the association of gender, age, and Parkinsonism symptoms with TRODAT imaging analysis and conclusions.

RESULTS

Table I summarizes the characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates.

Of the 16 patients, 10 were female and 6 were male, with an average age of 55.2 years (range: 26-75 years). Fisher's Exact Test (Table II) revealed a significant difference in qualitative TRODAT and overall scan findings between patients with and without tremor but no significant differences between gender, age, bradykinesia, and rigidity symptoms. The primary referral reasons for Tc-99m TRODAT-1 SPECT-CT varied among the patients. Most (62.4%) were referred for diagnosing idiopathic Parkinson's disease (IPD) in atypical presentations. Four patients (25.0%) were referred to exclude drug-induced parkinsonism, one patient (6.3%) to differentiate IPD from essential tremor, and another (6.3%) to exclude functional parkinsonism.

Figure 1 illustrates that the percentage of striatal asymmetry in normal DAT binding patterns ranged from 1.39% to 6.16% (mean 3.02%). In contrast, the abnormal DAT binding pattern displayed a broader range of striatal asymmetry, from 0.52% to 20.62% (mean 7.90%).

Five patients (31.3%) exhibited normal DAT binding patterns on the Tc-99m TRODAT-1 SPECT-CT. Based on clinical history and normal scintigraphy findings, one patient was diagnosed with essential tremor (Figure 2(i)), three with drug-induced parkinsonism (Figure 2(ii)), and one with functional parkinsonism. The remaining 11 patients (68.7%) with abnormal DAT binding, as assessed qualitatively and quantitatively by Tc-99m TRODAT-1 SPECT-CT, were confirmed to have striatal dopaminergic deficiency (Figure 3(i)). Among the 11 abnormal scans, three patients (27.3%) showed bilateral striatal DAT binding reduction, while eight (72.7%) exhibited asymmetrical DAT loss contralateral to the symptomatic side. Correlating these findings with clinical histories, six patients were concluded to have IPD. Qualitative and quantitative interpretations were concordant in all scans except for two patients with drug-induced parkinsonism, who showed a fairly symmetrical DAT binding pattern with slightly lower caudate SVR values. These discrepancies could be attributed to motion artifacts or non-specific uptake in Tc-99m TRODAT-1 scans. Five patients were recommended for further FDG PET imaging to aid in diagnosing atypical Parkinson's disease. Two of these patients underwent additional brain neuroimaging with FDG PET and both were diagnosed with corticobasal degeneration (CBD).

Reviewing our Tc-99m TRODAT-1 SPECT-CT reports, 13 patients (81.3%) experienced changes in therapeutic

management during follow-up. Our findings confirmed IPD in the majority of our patients (37.5%), leading to optimized anti-Parkinsonian medications for better disease control. Three patients (18.8%) received new anti-psychotic drugs following a diagnosis of drug-induced parkinsonism. One patient (6.3%), diagnosed with essential tremor based on clinical history and normal scintigraphy findings, was started on beta-blockers. Another patient (6.3%) with normal scintigraphy findings and functional parkinsonism was referred to a neuropsychiatrist for neurorehabilitation, resulting in recovery after three weeks. Two patients (12.5%) diagnosed with CBD based on Tc-99m TRODAT-1 SPECT-CT and FDG PET findings were treated accordingly.

DISCUSSION

Diagnosing IPD relies heavily on clinical symptoms such as bradykinesia, rigidity, resting tremor, postural instability, and response to levodopa therapy. Differentiating IPD from other parkinsonian-like syndromes is crucial for determining treatment options. This study primarily investigated the value of Tc-99m TRODAT-1 SPECT-CT in differentiating parkinsonism. Evaluating striatal DAT binding on Tc-99m TRODAT-1 SPECT-CT involves both qualitative visual interpretation of reconstructed SPECT images and quantitative analysis of the SPECT data. Our study found reduced striatal DAT binding in 11 out of 16 patients. Most patients (8) with abnormal scintigraphy demonstrated unilateral reduction at the contralateral striatum, prominently at the contralateral putamen. The remaining three patients showed bilateral striatum uptake reduction, suggesting advanced disease. Visual analysis included assessing asymmetrical striatum and differential radiotracer uptake in striatal subregions. The normal striatum appears symmetrical with a comma shape, clearly visualized in an axial cut (Figure 2(i)). However, slight asymmetry in striatal or striatal subregions may occur in less than 6% of healthy individuals.[17]

Decreased pre-synaptic dopaminergic function appears as unilateral or bilateral radiotracer uptake reduction in the striatum with high background activity in DAT SPECT images. Contralateral reduction of tracer uptake in the dorsal putamen relative to the clinically affected side is a common early finding in IPD, often presenting as a prominent unilateral posterior-to-anterior gradient loss.[17] This pattern aligns with many studies suggesting that the contralateral putamen is the most accurate region for differentiating between IPD and healthy individuals or essential tremor.[15] In early-stage IPD, the contralateral striatum typically appears oval or circular on a Tc-99m TRODAT-1 SPECT-CT scan due to severe putamen involvement.[33] As the disease progresses, it affects the ipsilateral putamen, followed by the contralateral caudate nucleus, and subsequently the ipsilateral caudate nucleus.[17] Therefore, bilateral striatum uptake reduction may be observed in advanced IPD cases.[17]

Quantitative analysis evaluates each striatal subregion and the degree of striatal asymmetry, particularly in complex and borderline cases.[17] We conducted quantitative analysis using a fully automated template on VOI analysis to quantify DVR of various striatal subregions, including the striatum, caudate and putamen. All these subregions were then normalized to the occipital cortex.[34] Our quantitative analyses were compared with a normal database provided by Weng et al., which proposed age-specific normal ranges of SBR for each striatal subregion.[35] However, for our two patients (aged 26 and 37), no database comparison was made due to the lower age limit of 50 years in Weng et al.'s study. Reporting for these patients was based primarily on qualitative analysis and subsequent follow-up with the primary team.

Weng et al. evaluated 78 consecutive IPD patients and 40 age-matched healthy subjects, finding high sensitivity and specificity of Tc-99m TRODAT-1 SPECT-CT in measuring DAT loss in IPD patients.[35] The study also highlighted an age-related decline in striatal binding in the healthy group.[35] Based on the similar parameter of image acquisition, Weng et al.'s age-specific normal range of SBR for each striatal subregion served as a reference for our patients with DAT-related disease to estimate DAT loss.[35] All our analyzed data for each striatal subregion were in DVR, converted to SBR before interpretation.

Hwang WJ et al. found a mean striatal asymmetry index of 12.62 ± 11.32 in IPD patients.[36] The normal TRODAT scan in our study showed a lower mean striatal asymmetry (3.02%) compared to the abnormal scan (7.90%). The range of striatal asymmetry in abnormal studies (0.52% to 20.62%) was significantly broader than in normal scans (1.39% to 6.16%). The lowest striatal asymmetry in abnormal scans (0.52%) was even lower than in normal scans (1.39%), indicating advanced disease. Higher striatal asymmetry reflects a greater decrease in contralateral striatal DAT binding, consistent with IPD. This highlights Tc-99m TRODAT-1 SPECT-CT's ability to distinguish IPD patients from other parkinsonian-like syndromes, except in advanced IPD.

Overall, there was concordance between qualitative and quantitative results. All substriatal values in normal and abnormal results fell within or below the reference range, respectively. However, two cases showed discrepancies between qualitative and quantitative analyses, likely due to motion artifacts or non-specific uptake in Tc-99m TRODAT scans.[35] Thus, quantitative analysis should be interpreted alongside visual analysis by an experienced reader.

In our study, five patients exhibited normal striatal DAT bindings, including one patient with essential tremor, three patients with drug-induced parkinsonism, and one patient with functional parkinsonism. These findings align with numerous recent studies demonstrating that Tc-99m TRODAT-1 SPECT-CT imaging serves as a marker for distinguishing IPD patients from healthy individuals or those with essential tremor.[15] Tc-99m TRODAT-1 SPECT-CT findings are typically normal in healthy individuals and in cases of non-neurodegenerative parkinsonism such as essential tremor (ET), psychogenic or functional parkinsonism, and drug-induced parkinsonism.[33] Consequently, these conditions can be differentiated from neurodegenerative Parkinsonian syndrome, which shows abnormal DAT imaging results. Tc-99m TRODAT-1 SPECT-CT images also exhibit high

Table I: Characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates

No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
1	55	Male	Schizophrenia on Olanzapine. Bilateral hand tremors (right > left) associated with hand tremor.	Bilateral striatum shows normal and symmetrical DAT binding.	1.3 N	1.22 N	1.14 N	1.34 N	1.68	Normal DAT binding pattern. The clinical tremor is likely secondary to drug induced Parkinsonism.	Drug induced Parkinsonism. Change the antipsychotic treatment.
2	72	Female	Schizophrenia on intramuscular Paliperidone injection. Bilateral lower limb weakness and bilateral upper and lower limb tremors.	Bilateral striatum shows normal and symmetrical DAT binding.	0.8 AB	0.81 AB	0.9 N	0.83 N	1.39	Normal DAT binding pattern.	Drug induced Parkinsonism. Change the antipsychotic treatment.
3	52	Female	Bradykinesia, resting tremor and rigidity of the limbs.	Asymmetrical severely reduced DAT binding of bilateral posterior putamen (severe on the right) and right caudate.	0.87 AB	0.48 AB	0.36 AB	0.19 AB	20.62	Abnormal DAT binding pattern. In correlation with clinical history, this findings is suggestive of IPD.	IPD. Optimisation of medication.
4	51	Male	Rigidity and resting tremor of right upper limb and bradykinesia.	Severely reduced DAT binding of bilateral caudate and putamen.	0.59 AB	0.51 AB	0.33 AB	0.48 AB	1.31	Abnormal DAT binding pattern. In correlation with clinical history, this findings is suggestive of IPD.	IPD. Optimisation of medication.
5	54	Male	Resting tremors over left upper and lower limb.	Asymmetrical reduced DAT binding of bilateral posterior putamen (severe on the right) and right caudate.	1.08 AB	0.8 AB	0.61 AB	0.4 AB	14.43	Abnormal DAT binding. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest for FDG PET if clinically indicated.	IPD. Patient defaulted treatment
6	56	Female	Presented with fall, imbalance while walking, weakness and rigidity of right upper and lower limb with micrographia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral posterior putamen (severe on the left) and left caudate.	0.43 AB	0.56 AB	0.19 AB	0.21 AB	6.70	Abnormal DAT binding. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	To exclude atypical Parkinson disease. For FDG PET CT.

Table I: Characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates

No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
7	60	Male	Paroxysmal head tremor, which emerge during high concentration activity or stressful situation	Bilateral striatum shows normal and symmetrical DAT binding.	1.38 N	1.28 N	1.1 N	1.09 N	2.46	Normal DAT binding pattern.	Essential tremor. Started on beta blocker.
8	26	Female	Unsteady gate, fall, slurred speech, occasional urinary incontinence, vertical gaze palsy, dysphagia and bradykinesia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral caudate and bilateral putamen.	0.33 AB	0.44 AB	0.26 AB	0.29 AB	5.65	Abnormal DAT binding pattern. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	To exclude atypical Parkinson disease. For FDG PET CT.
9	68	Female	Right sided hemiaprexia, severe dysarthria, emotional disability and dysphagia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral putamen (severe on the left) and left caudate.	0.67 AB	1.01 AB	0.19 AB	0.45 AB	19.00	Abnormal DAT binding pattern. FDG PET shows features of corticobasal degeneration.	Further evaluation with FDG PET CT confirmed the diagnosis of CBD.
10	69	Female	Initially presented with essential tremor. Symptom worsened with gait instability and bradykinesia.	Asymmetrical reduced DAT binding uptake of the bilateral posterior putamen, with significant reduction on the right.	0.72 AB	0.63 AB	0.42 AB	0.43 AB	3.52	Abnormal DAT binding pattern. In correlation with clinical history, this could likely suggest IPD.	IPD. Optimisation of medication.
11	37	Female	Bilateral lower limb tremor, unable to walk normally, slow speech and occipital headache. TRO functional parkinsonism.	Bilateral striatum shows normal and symmetrical DAT binding.	1.68 N	1.74 N	1.32 N	1.49 N	3.39	Normal DAT binding pattern. In correlation with clinical history, these findings are suggestive of functional Parkinsonism more likely than IPD.	Referred for Neurorehabilitation. Patient improved well.
12	42	Male	Bilateral rigidity, bradykinesia and axial rigidity associated with constipation and urinary urgency.	Reduced DAT binding of bilateral caudate and bilateral putamen.	0.57 AB	0.58 AB	0.29 AB	0.26 AB	0.52 AB	Abnormal DAT binding pattern. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	Further evaluation with FDG PET CT confirmed the diagnosis of CBD.

Table I: Characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates

No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
13	45	Male	Bradykinesia and cogwheel rigidity of bilateral upper limb.	Asymmetrical reduced DAT binding of bilateral caudate and putamen (severe on the right).	0.73 AB	0.56 AB	0.59 AB	0.55 AB	6.80	Abnormal DAT binding pattern.	IPD. Optimisation of medication.
14	75	Female	Schizophrenia (more than 30 years) with depression) on Paliperidone and T. Artane. Pill rolling tremor, bradykinesia, jaw tremor and cogwheel rigidity.	Bilateral striatum shows normal and symmetrical DAT binding.	0.84 AB	0.63 AB	0.73 N	0.75 N	6.16	Fairly symmetrical DAT binding pattern. Scan findings is suggestive of drug-induced Parkinsonism.	Drug induced Parkinsonism. Change the antipsychotic treatment and continue PD medication.
15	52	Female	Initially treated with IPD. Also presented with multiple falls due to imbalance and difficulty to initiate movements. Patient did not respond to treatment. TRO atypical parkinsonism.	Reduced DAT binding of bilateral caudate and bilateral putamen.	0.23 AB	0.23 AB	0.11 AB	0.04 AB	1.50	Abnormal DAT binding pattern indicating basal ganglia dysfunction. However, unable to differentiate between IPD or atypical PD. Suggest for FDG PET.	To exclude atypical Parkinson disease. For FDG PET CT.
16	69	Female	Bipolar disorder on Epilim and Olanzapine. Bilateral hand tremor (right more than left).	Asymmetrical reduced DAT binding of left putamen.	0.96 AB	0.92 AB	0.54 AB	0.91 N	6.80	Abnormal DAT binding pattern.	IPD. Optimisation of medication.

N: Normal
AB: Abnormal
TRO: To rule out

Table II: Association of gender, age and symptoms of Parkinsonism with TRODAT reporting

	Qualitative assessment of TRODAT		p-value	Quantitative assessment of TRODAT		p-value	Conclusion of TRODAT reporting		p-value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
Gender									
Female	3	7	1.0000	1	9	0.5179	3	7	1.0000
Male	2	4		2	4		2	4	
Age									
≤ 50	1	3	1.0000	1	3	1.0000	1	3	1.0000
> 50	4	8		2	10		4	8	
Tremors									
Yes	5	4	0.0337*	3	6	0.2125	5	4	0.0337*
No	0	7		0	7		0	7	
Bradykinesia									
Yes	2	7	0.5962	1	8	0.5500	2	7	0.5962
No	3	4		2	5		3	4	
Rigidity									
Yes	1	5	0.5879	0	6	0.2500	1	5	0.5879
No	4	6		3	7		4	6	

Fishers' Exact Test (p-value <0.05 indicated a significant difference)

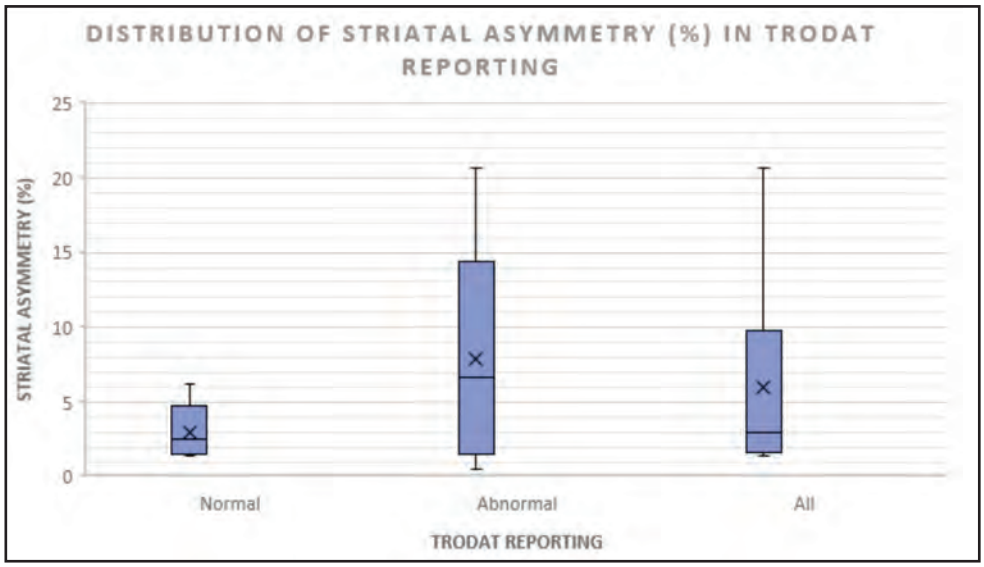

Fig. 1: Distribution of striatal asymmetry (%) in TRODAT reporting

sensitivity and negative predictive values in the early stages of IPD, which often presents with mild parkinsonism.[33] Both the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr stage scores, which assess the degree of motor impairment, have shown a strong correlation between the level of TRODAT-1 uptake and IPD severity, though this correlation diminishes once it reaches saturation in the later stages of the disease.[15,33] In advanced IPD cases, reduced tracer uptake is observed in all striatal subregions.[17] Interestingly, in IPD patients, the downregulation of DAT expression in remaining neurons leads to an overestimation of the true extent of neurodegeneration in the striatum on Tc-99m TRODAT-1 SPECT-CT imaging. This downregulation functions as an adaptive mechanism to preserve synaptic dopamine levels.[33]

Accurate differentiation of IPD from atypical Parkinsonian syndrome is crucial, as it impacts prognosis and treatment strategies. A study by Aghdam et al. found no significant differences in differentiating IPD from atypical Parkinsonian syndrome using either Tc-99m TRODAT-1 SPECT or its co-registration with MRI.[37] Conversely, another study utilizing Tc-99m TRODAT-1 SPECT with MRI volumetry was able to differentiate non-parkinsonian syndromes from IPD, although the non-parkinsonian syndromes were not pathologically verified.[38] Generally, FDG PET brain imaging has become the standard for distinguishing IPD from atypical Parkinsonism syndromes.[22-25] Five of our patients with abnormal scintigraphy findings were recommended for further evaluation for atypical Parkinsonian syndrome due to clinical presentations atypical for IPD. Only two patients consented to FDG PET, both demonstrating typical patterns of corticobasal degeneration (CBD) on FDG findings. In CBD, marked asymmetrical striatal involvement is observed in both the caudate nucleus and putamen on the Tc-99m TRODAT-1 SPECT study, which can be more pronounced on

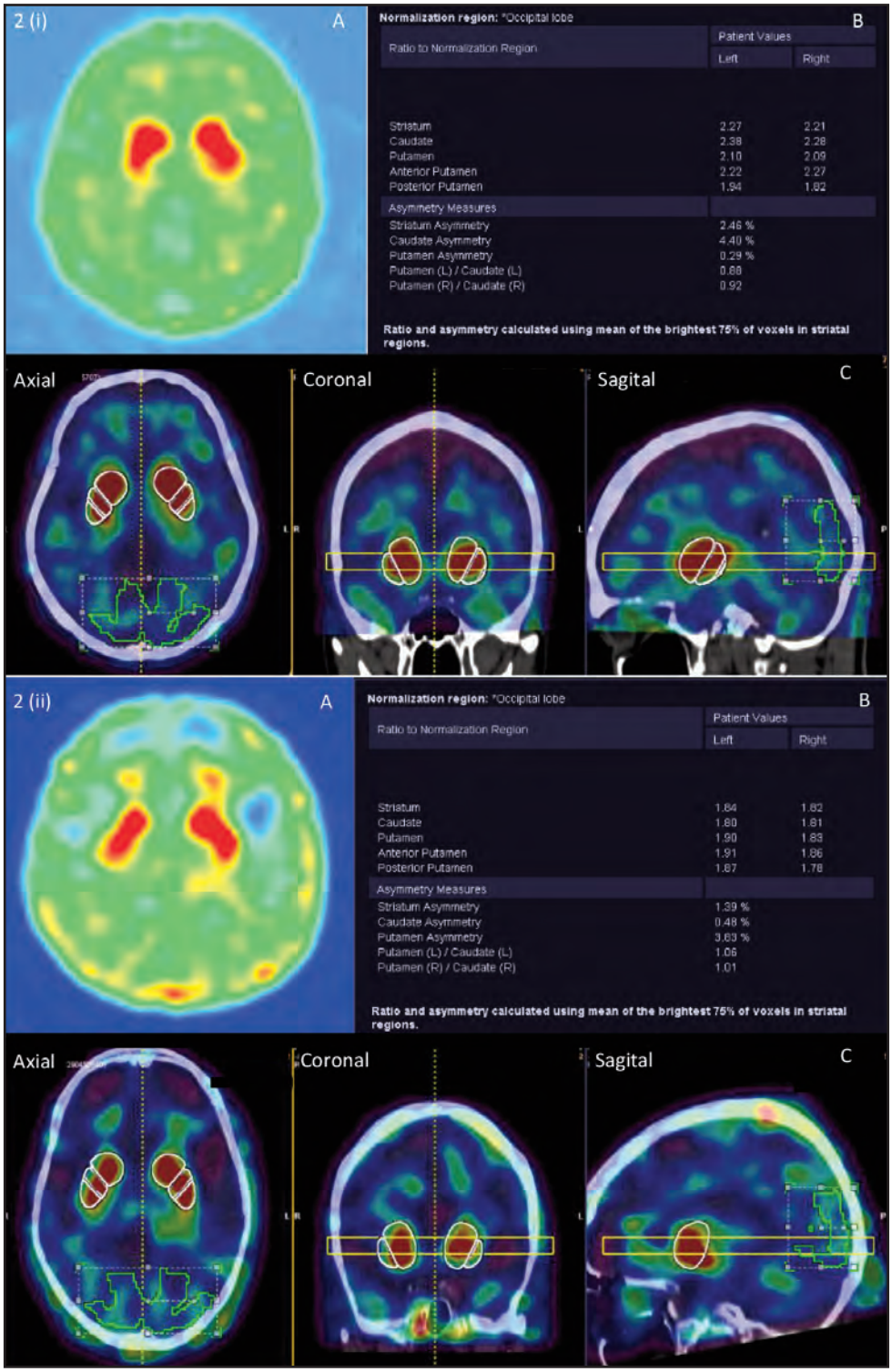

Fig. 2: (i). Tc-99m TRODAT-1 SPECT CT images of a 60-year-old man, presented with paroxysmal head tremors for 3 years with suspected essential tremor. The patient had an inconsistent response towards Benzhexol. (A) Transaxial TRODAT-1 SPECT-CT scan showed symmetrical and normal DAT striatal binding. Both striata have comma shapes and sharp borders. (B) and (C) Semiquantitative analysis based on automated VOI was in normal ranges. This finding excludes the presence of a striatal dopaminergic deficiency and is consistent with essential tremor

(ii). Tc-99m TRODAT-1 SPECT CT images of a 72-year-old female, known case of schizophrenia on 3-monthly Paliperidone injection, presented with bilateral hands and lower limb tremors as well as bilateral lower limb weakness. (A) Transaxial TRODAT-1 SPECT-CT scan showed symmetrical and normal DAT striatal binding. Both striata have comma shapes and sharp borders. (B) and (C) Semiquantitative analysis based on automated VOI was in normal ranges. This scan finding excludes the presence of a striatal dopaminergic deficiency and is consistent with drug-induced parkinsonism secondary to Paliperidone

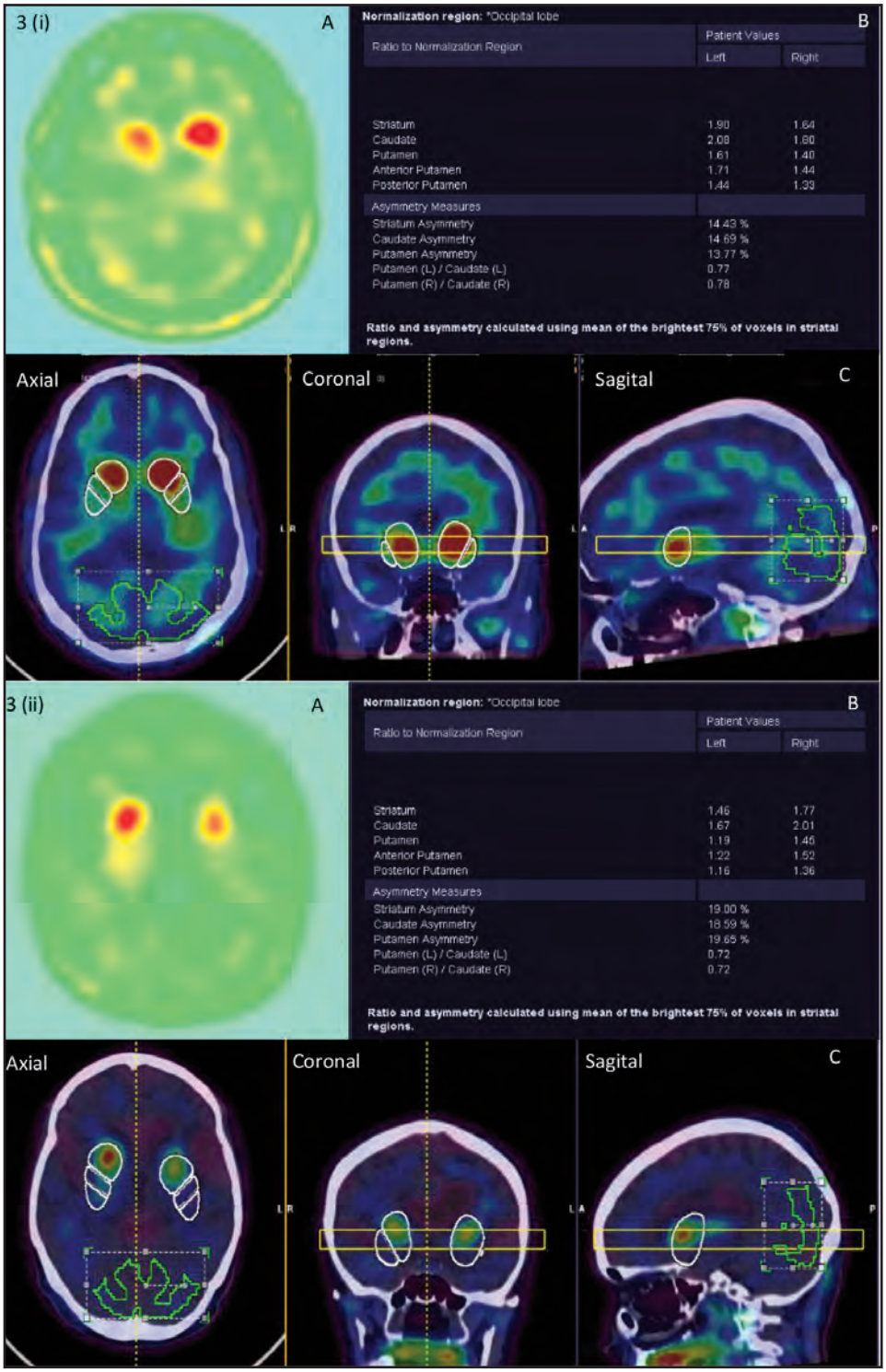

Fig. 3: (i). Tc-99m TRODAT-1 SPECT CT images of a 54-year-old male, presented with left leg cramping (predominantly at foot, ankle, and calf region), left hand resting tremor and left foot tremor. (A) Transaxial TRODAT-1 SPECT-CT scan showed reduced DAT binding of bilateral putamen and right caudate. Both striatum appear oval. (B) and (C) Specific binding ratios calculated from both putamen were significantly lower than the patient's age group. The striatal asymmetry index was 14.43%. These findings indicate the severe degree of nigrostriatal dopaminergic neuron loss and the pattern of involvement is suggestive of Idiopathic Parkinson's Disease

(ii). 68 year 68-year-old female presented with right-sided hemiaprexia, severe dysarthria, emotional disability, and dysphagia. (A) Transaxial TRODAT-1 SPECT-CT scan showed marked asymmetrical reduced DAT binding of bilateral putamen and left caudate. (B) and (C) Specific binding ratios calculated from both putamen and left caudate were significantly lower than the patient's age group. The striatal asymmetry index was 19%. Subsequent FDG PET CT as in Figure 3(iii)

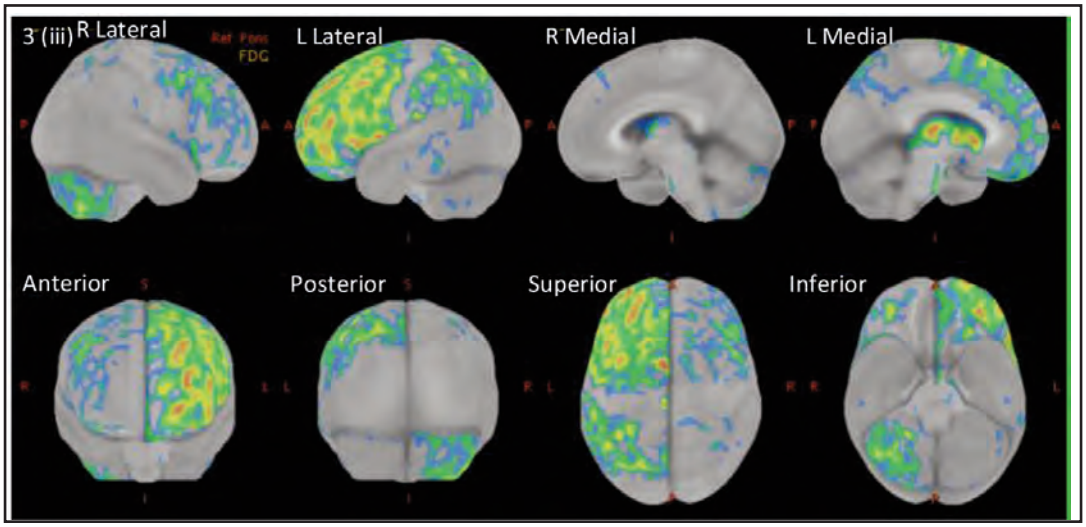

Fig. 3: (iii) Subsequent FDG PET-CT shows asymmetrical pattern of FDG hypermetabolism involving both frontoparietal cortices, more on the left

the side opposite to the clinically affected side (Figure 3(ii)).[33] This asymmetrical pattern of FDG hypometabolism was observed in both patients who underwent subsequent FDG PET CT scans (Figure 3(iii)).

However, a normal pattern of TRODAT uptake may also occur in patients with clinical corticobasal syndrome (CBS), likely due to underlying etiologies other than CBD, such as Alzheimer's disease or frontotemporal dementia. Patients with Lewy Body Dementia typically show early involvement of the caudate nuclei, leading to a less pronounced putamen-to-caudate gradient on TRODAT SPECT.[33] Similarly, early involvement of the anterior striatum is observed in the Parkinsonian subtype of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) compared to IPD.[33] The Parkinsonian subtype of MSA has less DAT function than the cerebellar subtype of MSA.[33] Although atypical Parkinsonian syndromes generally cause symmetrical involvement of the striatum compared to IPD, TRODAT-1 SPECT imaging alone may not sufficiently differentiate between different types of atypical Parkinsonian syndromes.[33]

Interestingly, in our study, one patient was diagnosed with neurodegenerative parkinsonian syndrome at the age of 23. Although rare in the young population, less than 5% of IPD cases present before age 50, termed early-onset IPD. Early-onset IPD is subdivided into juvenile PD (JPD), with onset before 21, and young-onset PD (YOPD), with onset between 21 and 40.[39-40] Due to atypical symptoms and abnormal imaging findings, this patient was referred for further FDG PET imaging, but patient defaulted.

All scintigraphy findings were communicated to our referring teams, and patients were followed up in subsequent clinic reviews after the Tc-99m TRODAT-1 SPECT-CT scan. Based on post-scan clinical updates, we observed a high percentage (81%) of changes in medical treatment following the Tc-99m TRODAT-1 SPECT-CT scan. This finding aligns with studies by Arjona M et al. and Catafau et al., which reported treatment changes of 75% and 72%, respectively.[13] Similarly, a study by Mirpour S et al. reported changes in management, including initiating new dopaminergic treatment, optimizing medication, and discontinuing dopaminergic drugs.[38] In our study, for abnormal scan findings, neurologists optimized anti-Parkinsonian drugs or requested further FDG PET-CT imaging to exclude atypical Parkinson's disease. For normal scan findings, neurologists excluded neurodegenerative causes of parkinsonism and treated patients accordingly. For instance, patients with essential tremors were prescribed beta blockers, and drugs causing parkinsonism in patients diagnosed with antipsychotic-induced parkinsonism were withheld. These findings underscore the important role of Tc-99m TRODAT-1 SPECT-CT scans in guiding physicians toward accurate clinical diagnoses of various parkinsonian syndromes and appropriate treatment choices. Additionally, Tc-99m TRODAT-1 SPECT-CT findings may lead to referrals for further FDG PET imaging for specific diagnoses of parkinsonian syndromes.

Our study had a few limitations. First, our sample size was small, and all patients were from a single institution. There was no established database for age-specific normal ranges for striatal binding ratios in our population, so we used the normal range from Weng et al. to interpret our quantitative data. However, this database is limited to a lower age limit of 50 and could not be utilized for early-onset parkinsonian syndrome. Lastly, our study lacked a control group to prove the clinical utility of this scan in influencing clinical decision-making.

CONCLUSION

Tc-99m TRODAT-1 SPECT-CT is a widely accessible tool for evaluating presynaptic dopamine transporters in parkinsonism patients. Despite some overlap in disease patterns between idiopathic Parkinson's disease (IPD) and

atypical Parkinsonian syndromes, normal Tc-99m TRODAT-1 SPECT-CT findings can effectively exclude non-neurodegenerative conditions like essential tremor (ET), drug-induced parkinsonism, and functional parkinsonism. For more precise differentiation of Parkinsonian syndromes, further imaging with FDG PET is recommended. Our study highlights the need for age-specific normal ranges for striatal binding ratios, underscoring the importance of further research in this area. This would enhance the diagnostic accuracy of Tc-99m TRODAT-1 SPECT-CT, particularly in diverse populations. Future research should focus on larger, multi-center studies to validate these findings and establish comprehensive normative data.

REFERENCES

1. Brooks DJ. Molecular imaging of dopamine transporters. Ageing Res Rev 2016; 30: 114-21.
2. Miller DB, O'Callaghan JP. Biomarkers of Parkinson's disease: present and future. Metabolism 2015; 64: 40-6.
3. Lim SY, Tan AH, Ahmad-Annuar A, Klein C, Tan LC, Rosales R et al. Parkinson's disease in the Western Pacific Region. Lancet Neurol 2019; 18: 865-79.
4. Yeh SHH, Tsai CJ, Yu TH, Chiang YH, Lin SZ, Peng NJ et al. 99mTc-TRODAT-1 SPECT revealed that striatal dopamine transport availability significantly decreases in late mid-aged healthy Taiwanese and then remains stable. Clin Nucl Med 2022; 47: 201.
5. Mozley PD, Acton PD, Barraclough ED, Plössl K, Gur RC, Alavi A et al. Effects of age on dopamine transporters in healthy humans. J Nucl Med 1999; 40: 1812–7.
6. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181-4.
7. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 2001; 57: 1497-9.
8. Brooks DJ. Technology insight: imaging neurodegeneration in Parkinson's disease. Nat Clin Pract Neurol 2008; 4: 267-7.
9. Berg D, Siefker C, Becker G. Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. J Neurol 2001; 248: 684-9.
10. Rao SS, Hofmann LA, Shakil A. Parkinson's disease: diagnosis and treatment. Am Fam Physician 2006; 74: 2046-54.
11. Fazio P, Svenningsson P, Cselenyi Z, Halldin C, Farde L, Varrone A. Nigrostriatal dopamine transporter availability in early Parkinson's disease. Mov Disord 2018; 33: 592-9.
12. Utiumi MA, Felício AC, Borges CR, Braatz VL, Rezende SA, Munhoz RP et al. Dopamine transporter imaging in clinically unclear cases of parkinsonism and the importance of scans without evidence of dopaminergic deficit (SWEDDs). Arq Neuropsiquiatr 2012; 70: 667-73.
13. Arjona M, Toldo JM, Queiroz NC, Pedroso JL, Neto GDCC, Barsottini OG et al. A real-world study of cerebral 99mTc-TRODAT-1 single-photon emission computed tomography (SPECT) imaging of the dopamine transporter in patients with Parkinson disease from a tertiary hospital in Brazil. Med Sci Monit 2020; 26: 925130-1.
14. Kraemmer J, Kovacs GG, Perju-Dumbrava L, Pirker S, Traub-Weidinger T, Pirker W. Correlation of striatal dopamine transporter imaging with post-mortem substantia nigra cell counts. Mov Disord 2014; 29: 1767–73.
15. Sasannezhad P, Juibary AG, Sadri K, Sadeghi R, Sabour M, Kakhki VR et al. 99mTc-TRODAT-1 SPECT imaging in early and late-onset Parkinson's disease. Asia Oceania J Nucl Med Biol 2017; 5(2): 114.
16. Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Nagren K et al. EANM procedure guidelines for brain neurotransmission SPECT using (123) I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2010; 37: 443-50.
17. Morbelli S, Esposito G, Arbizu J, Barthel H, Boellaard R, Bohnen NI et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. Eur J Nucl Med Mol Imaging 2020; 47: 1885-912.
18. Subramaniam RM, Frey KA, Hunt CH, Mercier GA Jr, Solnes LB, Colletti PM et al. ACR-ACNM practice parameter for the performance of dopamine transporter (DaT) single photon emission computed tomography (SPECT) imaging for movement disorders. Clin Nucl Med 2017; 42: 847-52.
19. Djang DS, Janssen MJ, Bohnen N, Booij J, Henderson TA, Herholz K et al. SNM practice guideline for dopamine transporter imaging with 123I-ioflupane SPECT 1.0. J Nucl Med 2012; 53: 154-63.
20. Lee JD, Huang CH, Weng YH, Lin KJ, Chen CT. An automatic MRI/SPECT registration algorithm using image intensity and anatomical feature as matching characters: application on the evaluation of Parkinson's disease. Nucl Med Biol 2007; 34: 447-57.
21. Dresel SH, Kung MP, Plössl K, Meegalla SK, Kung HF. Pharmacological effects of dopaminergic drugs on in vivo binding of [99mTc] TRODAT-1 to the central dopamine transporters in rats. Eur J Nucl Med 1998; 25: 31-9.
22. Hellwig S, Amtage F, Kreft A, Buchert R, Winz OH, Vach W et al. 18F-FDG-PET is superior to 123I-IBZM-SPECT for the differential diagnosis of parkinsonism. Neurology. 2012; 79: 1314-22.
23. Nicastro N, Garibotto V, Burkhard PR. The role of molecular imaging in assessing degenerative parkinsonism – an updated review. Swiss Med Wkly 2018; 148:14621.
24. Peralta C, Strafella AP, Van Eimeren T, Ceravolo R, Seppi K, Kaasinen V et al. International Parkinson Movement Disorders Society-Neuroimaging Study Group. Pragmatic approach on neuroimaging techniques for the differential diagnosis of parkinsonism. Mov Disord Clin Pract 2022; 6-19.
25. Guedj E, Varrone A, Boellaard R, Albert NL, Barthel H, Van Berckel B et al. EANM procedure guidelines for brain PET imaging using [18F] FDG, version 3. Eur J Nucl Med Mol Imaging 2022; 1-20.
26. Huang WS, Lin SZ, Lin JC, Wey SP, Ting G, Liu RS. Evaluation of early-stage Parkinson's disease with Tc99m TRODAT-1 imaging. J Nucl Med 2001; 42:1303-8.
27. Guttman M, Burkholder J, Kish SJ, Hussey D, Wilson A, DaSilva J et al. 11C-RTI-32 PET studies of dopamine transporter in early dopamine-naïve Parkinson's disease: implication for the symptomatic threshold. Neurology 1997; 48:1578-83.
28. Wilson JM, Levey Al, Rajout A, Ang L, Guttman M, Shannak K et al. Differential changes in neurochemical markers for striatal dopamine nerve terminals in idiopathic Parkinson's disease. Neurology 1996; 47: 718-26.
29. Huang WS, Chiang YH, Lin JC, Chou YH, Cheng CY, Liu RS. Crossover study of [99mTc]-TRODAT-1 SPECT and 18F-FDOPA PET in Parkinson's disease patients. J Nucl Med 2003; 44:999-1005.
30. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591-601.
31. Chou KL, Hurtig HI, Stern MB, Colcher A, Ravina B, Newberg A et al. Diagnostic accuracy of [99mTc] TRODAT-1 SPECT imaging in early Parkinson's disease. Parkinsonism Relat Disord 2004; 10: 375-9.
32. Uhl GR. Neurotransmitter transporters (plus): a promising new gene family. Trends Neurosci 1992; 15: 265-8.
33. Akdemir ÜÖ, Bora HAT, Atay LÖ. Dopamine transporter SPECT imaging in Parkinson's disease and Parkinsonian disorders. Turk J Med Sci 2021; 51: 400-10.
34. Fahmi R, Platsch G. White paper: Striatal analysis in syngo. via MI Neurology. Siemens Healthc GmbH 2020.

35. Weng YH, Yen TC, Chen MC, Kao PF, Tzen KY, Chen RS et al. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. J Nucl Med 2004; 45(3): 393-401.
36. Hwang WJ, Yao WJ, Wey SP, Ting G. Reproducibility of 99mTc-TRODAT-1 SPECT measurement of dopamine transporters in Parkinson's disease. J Nucl Med 2004; 45(2):207-13.
37. Aghdam ZB, Tabrizi SN, Arasteh A, Khalafi M, Ghojazadeh M, Mahmoudian B. Diagnostic evaluation of 99mTc-TRODAT-1 SPECT in parkinsonism. J Res Clin Med 2021; 9:36.
38. Mirpour S, Turkbey EB, Marashdeh W, El Khouli R, Subramaniam RM. Impact of DAT-SPECT on management of patients suspected of parkinsonism. Clin Nucl Med 2018; 43: 710–4.
39. Niemann N, Jankovic J. Juvenile parkinsonism: differential diagnosis, genetics, and treatment. Parkinsonism Relat Disord 2019; 67: 74-89.
40. Arena JE, Fonseca MM, Pinto Júnior HA, da Silva AA, Barbosa ER. Correlation between 99mTc-TRODAT-1 SPECT and 18F-FDOPA PET in patients with Parkinson's disease: a pilot study. Radiol Bras 2021; 54: 232-7.

Cardiac manifestations of post-acute withdrawal syndrome from a history of synthetic cathinone and opioid use

Ainur Shukimbayeva[1], Maria Prilutskaya, PhD[2], Jamila Mansurova, PhD[3]

[1]Pavlodar Branch of the Non-Commercial Joint-Stock Company Semey Medical University, Republic Scientific and Practical Centre for Mental Health, Toraigyrov St. 72/1, Pavlodar, Kazakhstan, [2]Pavlodar Branch of the Non-Commercial Joint-Stock Company Semey Medical University, Republic Scientific and Practical Centre for Mental Health, Toraigyrov St. 72/1, Pavlodar, Kazakhstan, [3]Non-Commercial Joint-Stock Company "Semey Medical University", Abay St. 103, Semey, Kazakhstan

ABSTRACT

Introduction: Synthetic cathinones and opioids are among the most commonly used illicit drugs in Central Asia, including Kazakhstan. Despite the advent of synthetic cathinones, opioids have not lost their relevance. Patients frequently report poly-dependence, combining cathinones and opioids. The use of synthetic cathinones and opioids is associated with cardiovascular disease and cardiovascular mortality. However, there is limited data describing the cardiac effects of synthetic cathinones and opioids in patients with post-acute withdrawal syndrome. The aim of this work is to describe and compare the cardiac manifestations in patients using synthetic cathinones and opioids with post-acute withdrawal syndrome.

Materials and Methods: In this case-control study, we examined 294 patients over the age of 18 who were using synthetic cathinones and opioids. All patients underwent electrocardiography and transthoracic echocardiography.

Results: Our study involved 183 patients using synthetic cathinones and 111 patients reporting opioid use. The average age of the patients was 32.4 ± 8.5 years. In patients using synthetic cathinones, electrocardiography showed a lengthening in the average duration of the ventricular QRS complex (70.5 ± 13.3 ms vs. 69.6 ± 11.7 ms), T wave (154.1 ± 27.5 ms vs. 140.4 ± 24.1 ms), and QT interval (338.2 ± 28.5 ms vs. 334.8 ± 33.5 ms), as well as a shortening of the P wave (79.1 ± 12.2 ms vs. 82.6 ± 14.4 ms) and PQ interval (146.4 ± 19.6 ms vs. 148.3 ± 20.1 ms). Echocardiography confirmed left ventricular hypertrophy in 10.9% of the synthetic cathinones group and 17.1% of the opioid group. Transmitral left ventricular diastolic dysfunction was diagnosed in 23.5% of patients in both groups. Additionally, 31.1% of patients using synthetic cathinones and 44.1% of those using opioids had a reduced ejection fraction on echocardiography.

Conclusion: In patients using synthetic cathinones the QT interval was longer compared to those using opioids. The ejection fraction was lower in the opioid group. Electrocardiographic and echocardiographic screening should be conducted for all patients with post-acute withdrawal syndrome to prevent life-threatening arrhythmias and heart failure.

KEYWORDS:
Synthetic cathinones, opioids, cardiac symptoms, post-acute withdrawal syndrome

INTRODUCTION

New psychoactive substances (NPS) are a large group of recreational drugs, widely distributed under the guise of "legal" substances. NPSs are analogues of the main narcotic substances or a imitation of already existing psychoactive chemical compounds. Currently, more than 950 substances are known.[1] There is a growing interest in NPSs among young and adolescent drug users due to their availability, diversity and relative affordability. All this creates concerns in the health care system, in education, and in law enforcement agencies.[2]

Synthetic cathinones (SC) are one of the most prevalent and particularly popular chemical group among other NPSs. SC were first synthesized in 1928.[3] In the countries of Central Asia on the drug market SC appeared since 2015.[4] In these countries one of the most popular SCs are α-pyrrolidinovalerophenone (α-PVP) and 4-methylmethcathinone (mephedrone) according to the reports of law enforcement agencies. Clandestine laboratories illegally manufacturing α-PVP and mephedrone are also a warning sign of the popularity of synthetic stimulants in the Central Asian region. For instance, Kazakhstan police reported about a manufacturing facilities that produced alpha-PVP and mephedrone for various territories of the country. Both alpha-PVP and mephedrone are listed as illegal drugs in Kazakhstan legal acts since the end of the 2010-s. Worldwide, these two substances were classified as hazardous drugs throughout more than a hundred countries and territories. Mephedrone was brought under Schedule II of the 1971 Convention on Psychotropic Substances at the 58th Commission on Narcotic Drugs (CND) in Vienna in 2015.[5] The following year, alpha-PVP was scheduled after the series of risk assessment by European Monitoring Centre for Drugs and Drugs Addiction and United Nations Office on Drugs and Crime.[6] Official documents notified a myriad of SC side effects and health risks.

Pharmacological profiles these SCs vary significantly. α-PVP is a pyrovalerone derivative that exhibits strong dopamine transporter and norepinephrine transporter inhibition, but

This article was accepted: 23 September 2024
Corresponding Author: Ainur Shukimbayeva
Email: ainur.shukimbayeva@smu.edu.kz

negligible serotonin transporter inhibition and negligible releasing properties.[7] Mephedrone is nonselective substrates for plasma membrane monoamine transporters, produces increases in extracellular dopamine and serotonin.[8] Due to these pathways indirect sympathomimetics effects entail a wide range of cardiovascular abnormalities.

Chest pain, tachycardia, hypertension are the main cardiac symptoms in those who use SC during the intoxication period.[9,10] Cases of myocardial infarction with ST segment elevation and multiple blood clots, atrial fibrillation, and cardiac arrest have been reported with alpha-PVP and mephedrone use.[11–13]

Opioids also remain the most commonly used illicit drugs in the Central Asia including Kazakhstan. Opioid using associated with cardiovascular disease and cardiovascular mortality.[14] With the advent of synthetic stimulants, opioids have not lost their relevance. Patients very often report poly-dependence with a combination of cathinones and opioids.[15]

Over the course of SC and opioid regular use, the period of withdrawal begins between 24 hours to 7 days following the last use of NPS.[16] During this period cardiac symptoms may be the same as in intoxication.[17] The post-acute withdrawal syndrome (PAWS) occurs after substance withdrawal and can last up to two months.[17] As of today, in our current knowledge, there has been no studies on the comparing chronic effects of SC and opioid on the cardiovascular system of patient with PAWS. This can cause difficulties in the clinician's understanding of the features of differential diagnosis. Therefore, this study describe and compare the clinical data of patients using SC and opioid with PAWS.

MATERIALS AND METHODS

In our case-control design of study, over a period of six months, we examined 294 patients over 18 years of age who were hospitalized at the Mental Health Center for rehabilitation due to chronic dependence on NPS (α-PVP and mephedrone) and opioid. We screened history cases for the presence of diagnostic code F15 (other stimulant related disorders) and F11 in ICD-10. In our study patients were included if they reported a history of SC and opioid use and those patients who indicated that more than 7 days had passed since their last substance use. Local Ethical Commission approval was obtained from Semey Medical University for conducting this study (Protocol No. 2 of 10/28/2020). All patients signed an informed consent form. Patients were excluded if they had clinical manifestations cardiovascular diseases (e.g., edema).

All patients underwent an express drug test (The NarcoCheck®) upon admission to the hospital. This test strip was made for the rapid detection in human urine of mephedrone and α-PVP. This test was positive if the sample tested contains at least 500 nanograms of mephedrone and α-PVP per milliliter of urine. The patients were also tested during hospitalization using an express test panel (morphine, tramadol).

Patients were asked about their use of all prohibited drugs (also about use of other sympathomimetic drugs, amphetamines, cocaine), mean duration of SC, opioid use, the maximum daily dose, and the way of drug administration. Data was collected on nicotine smoking, alcohol consumption, as well as complaints regarding the cardiovascular system.

For all patients, blood pressure (BP) was measured at the shoulder and ankle, and the ankle-shoulder index (ASI) was calculated. A cardiac auscultation was performed.

Indicators of the complete blood count and laboratory results of glucose, liver, kidneys function studies were obtained from the case histories. All patients underwent electrocardiography (ECG) on the Nihon Kohden Cardiofax S machine. ECG was interpreted by manual calculations. ECG was done by one investigator. All calculations of waves, intervals were carried out in milliseconds.[18] The sinus bradycardia was determined by heart rates below 60 beats per minute, and the sinus tachycardia by heart rates above 100 beats per minute. Early ventricular repolarization was diagnosed in the presence of concave ST segment elevation, notching at the point J, and asymmetric T waves on the ECG. It has been determined that left ventricular hypertrophy occurs when the Cornell index (R in avL + S in V3) is greater than 28 mm in men, and greater than 20 mm in women.

Transthoracic echocardiography (ECHO CG) was performed in all patients using the SonoScape SSI-6000. The measurements were taken in the parasternal and apical positions in millimeters. In the parasternal position the interventricular septum, the thickness of the posterior wall of the left ventricle (normal values: 6-10 mm), the end-diastolic (EDD) (normal values: 42-58.4 mm) and the end-systolic dimensions (ESD) (normal values: 25-39.8 mm), and aortic parameters were measured. PW and CW Doppler have been used to quantify blood flow velocity. Color Doppler was used to assess the nature of the blood flow. E/A ratio less than 0.8 confirms the existence diastolic dysfunction. The ejection fraction (normal values: >55%), end-diastolic (EDV) (normal values: 62-150 ml), end-systolic volumes (ESV) (normal values: 21-61 ml), stroke volume (SV) (normal range is 50 to 100 ml) of the left ventricle were assessed in the M-mode according to Teicholz. Right ventricular systolic function was assessed using fractional area change tricuspidannular plane systolic excursion (TAPSE normal values: >0.7cm).[19]

The IBM SPSS Statistics 20 program was used to perform descriptive analysis of quantitative and qualitative variables (percentage, mean M, and standard deviation SD). The t-test the Mann-Whitney U test were used to compare the quantitative data. The chi-square test was used to compare categorical data.

RESULTS

Our study involved 183 patients using α-PVP, mephedrone and 111 patients reporting opioid use. The average age of patients was 32.4±8.5 years. The male sex prevailed (87.4%) over the female (12.6%). 84.2% of patients used SC intranasaly or by smoking, 71.2% used opioids

Table I: Patient demographics. clinical characteristics and laboratory studies

	SC users n=183	opioid users n=111	p
Age, average (SD)	29.3(6.2)	35.6(10.8)	<0.0001
Intranasaly using or by smoking, n(%)	154(84.2)	-	<0.0001
Intravenously using, n(%)	27(14.8)	79(71.2)	<0.0001
using of tablets, n(%)	2(1)	32(28.8)	<0.0001
Maximum daily dose of the substance **, average (SD)	1.4(1.8)	12.7(6.6)	<0.05
Cardiac symptoms, n(%):	143(78.6)	49(44.1)	<0.0001
palpitations, n(%)	124(67.8)	28(25.2)	<0.0001
a feeling of lack of air, n(%)	83(45.4)	34(30.6)	<0.05
ALT, IU/L, average (SD)	40(81.9)	46.2(38.6)	<0.05
AST, IU/L, average (SD)	20.8(15.8)	42.8(45.2)	<0.0001

*-years
**-grams
ALT - alanine aminotransferase
AST - aspartate aminotransferase

Table II: ECHOCG results

	SC users n=183	opioid users n=111	p
The thickness of the posterior wall, mm, average (SD)	8.4(1.8)	9.2(2.1)	<0.05
Interventricular septum, mm, average (SD)	8.4(1.9)	9(2.1)	0.1
EDD, mm, average (SD)	43.9(8.3)	44.2(8.5)	<0.05
EDV, ml, average (SD)	89.3(34.7)	90.9(33.8)	<0.05
ESD, mm, average (SD)	28.6(7)	30.8(6.6)	0.7
ESV, ml, average (SD)	37.6(17.2)	39(18.1)	0.5
SV, ml, average (SD)	50.9(16.9)	51(17.7)	<0.05
E/A on TV, average (SD)	1.05(0.2)	1.02(0.2)	<0.05
E/A on MV, average (SD)	1.5(0.5)	1.4(0.5)	0.6
Ejection fraction for ECHO CG, %, average (SD)	58.8(7.8)	56.6(8.1)	<0.05
TAPSE, sm, average (SD)	2.4(0.3)	2.3(0.3)	<0.05

SD - standard deviation, SV – stroke volume, EDD - end-diastolic dimension, ESD - end- systolic dimension, EDV - end-diastolic volume, ESV - end- systolic volume, TV - tricuspid valve, MV – mitral valve, TAPSE - tricuspid annular plane systolic excursion.

intravenously. The last use of SCs was 1.2±1.3 months ago, opioids – 1.2±1.7. The average experience of SC uses was 3.9±3.5 years, opioid – 13.2±8.5. (Table I). Nicotine smoking among groups occurred in 92.5%. 19.7% of patients recovered from alcohol dependence.

65.5% of patients presented cardiac symptoms either during using and in withdrawal period. The leading symptoms were palpitations (51.7%) and a feeling of lack of air or shortness of breath (39.8%) (Table I). A stabbing type of pain was experienced in groups with SC (17.5%), 10.8% - with opioids. A pressing type of pain was experienced in 8.7% of cases with SC, 9% - with opioids. Patients reported that the duration of chest pain was observed to be between two and five minutes. The time of chest pain onset varied by substance with chest pain starting during only acute intoxication with alpha-PVP and only withdrawal syndrome with mephedrone. During the PAWS cardiac symptoms were fully resolved.

The average systolic blood pressure (SBP) on the arm in groups with SC was 124.1±11.8 mmHg, with opioid - 126.4±18.5 mmHg, diastolic blood pressure (DBP) with SC – 81.1+6.8 mmHg, opioid - 80.9±10.9 mmHg. On the leg, the SBP in first group was 143.6±19.4 mmHg, second - 143.9±21.9 mmHg and the DBP – 89.1±12.7 mmHg and 89.8±12.4 mmHg. The ASI was equal to 1.1±0.5 in SC group and 1.1±0.2, which corresponds to the limits of acceptable values. The number of heartbeats was equal to the pulse and 80±15.2 beats per minute were noted in both groups.

In the complete blood count, the indicators were within the reference range. The average blood glucose was 87.1 mg/dL±14.9, creatinine was 0.8 mg/dL±0.1, urea was 25.9 mg/dL±7.9. Laboratory results revealed an increase in the level of aspartate aminotransferase (AST) above 40 IU/L was noted in 18.0 % in group with SC, 30.6% - with opioids, and alanine aminotransferase (ALT) – 24.6% and 30.6% (value up to 40 IU/L was normal for our laboratory) (Table I).

In patients using SC, the ECG showed a lengthening of the average duration of the ventricular QRS complex (70.5±13.3 ms and 69.6±11.7 ms), T wave (154.1±27.5 ms and 140.4±24.1 ms), QT interval (338.2±28.5 ms and 334.8±33.5 ms), a shortening of the P wave (79.1±12.2 ms and 82.6±14.4 ms), PQ interval (146.4±19.6 ms and 148.3±20.1 ms). Sinus tachycardia was found in groups with SC in 3.8%, with opioid in 4.5%, bradycardia in 11% and 8.1%. Early ventricular repolarization syndrome was observed in groups with SC in 8.2 % of cases and with opioid in 6.3%. In 7.1% of cases there were signs of hypertrophy of the left ventricle in groups with SC, 9% - with opioids. Conduction disturbance in the form of a blockage of the right leg of the Gis beam was found in

14.8% in groups with SC, 13.5% - with opioids. Atrioventricular blockage of the I degree was found in one case in each group.

On ECHO CG left ventricular hypertrophy was confirmed in 10.9% in groups with SC, 17.1% - with opioids. Mitral regurgitation of the second degree occurred in 0.5% in first group, 2.7% in second group (0 and 1 degrees are acceptable values). Tricuspid regurgitation of the second degree occurred in 1.1% in groups with SC, 0.9% - with opioids. Transmittal left ventricular diastolic dysfunction was diagnosed in 23.5% in each group. 31.1% of patients on ECHOCG had a reduced ejection fraction in groups with SC, 44.1% - with opioids. Systolic function of the right ventricle was normal in both groups (Table II).

DISCUSSION

To our knowledge this study provides for the first time an in-depth description and comparison of the clinical manifestations of the cardiovascular abnormalities in 294 patients who used SC and opioid with PAWS.

In our clinical study, male patients predominated, which does not contradict the data of other studies.[20,21] Our study found an average age of group SC users is 29.3±6.2 years, opioid users - 35.6±10.8 years, which corresponds average age of patients in other studies.[20,21]

Patients who use illicit drugs have CVD risk factor. Smoking nicotine is one of the leading risk factors for CVD.[22] In our study, 92.5% of participants reported regular smoking.

NPSs are found in the form of powders, tablets, capsules. Oral, intranasal (nasal inhalation) prevail, less often intramuscular / intravenous, rectal method of administration are used.[23,24] It is known that when smoking and inhaling, the effect occurs faster even with a small dose of NPSs.[2] In our study, the intranasal method for mephedrone and smoking for α-PVP prevailed. Most often, the intravenous method is used by those who use heroin.[23] In our study the intravenous method and using of tablets dominate in the group of patients with opioids.

Tachycardia and hypertension are the main cardiac effects of SC use. While one of the symptoms of opioid withdrawal syndrome is tachycardia.[25] According to our ECG study, sinus tachycardia and bradycardia were detected in 3.8% and 11% in group with SC, with opioid in 4.5% and 8.1% of subjects, respectively. Probably bradycardia was associated with the absence of a period of SC and opioid intoxication.

QT interval was matters of great importance because of the relationship between prolongation of this and lethal ventricular arrhythmias.[18,25] Prolongation of the QT interval with the development of life-threatening arrhythmias on the ECG may be a consequence of the direct toxic effect of SC on cardiomyocytes.[26,27] To the best of our knowledge, there has been no studies on the chronic effects of α-PVP and mephedrone on ECG alterations of patient with PAWS. A study of B. Ünübol with 90 patients experienced opioid withdrawal and PAWS revealed QT interval prolongation. In contrast, our study discovered higher QT value in patients with SC, which was shorter than normal limits.[18]

Remodeling of the left ventricle can occur, as a result, of the sympathomimetic effect of SC with prolonged and continuous use.[28] There is no probable evidence of the effect of opioids on left ventricular remodeling.[29] In our small observation, we diagnosed hypertrophy of the left ventricle on the ECHO CG in 10.9% in groups with SC, 17.1% - with opioids. A study of M. Selcuk with 85 individuals, where 45 patients smoking heroin, experienced an increase in right ventricular diameter in the opioid group.[29] In our study there are no differences in the diameter of the heart chambers.

The first study of the effect of mephedrone on the heart muscle in 2012 experienced an the development of myocardial ischemia assosiated with cardiac arrest with high contractility.[24] Although heroin use does not have any effect on left ventricular function,[29] according to the our study 31.1% of patients had a situation between normal and reduced ejection fraction in groups with SC, 44.1% - with opioids. To the best of our knowledge, there has been no studies of left ventricular diastolic function in patients using SC. Left ventricular diastolic dysfunction was diagnosed by us in 23.5% in each group.

To our knowledge, this is the first description of clinical cardiac manifestations on the example of a case-control design study of chronic use of SC and opioid in the post withdrawal period. The description of the cases of chronic use of SC and opioids in the post withdrawal period partially demonstrates clinical manifestations of the cardiovascular abnormalities. Limitations of the work include the difficulties in laboratory identification cases of NPS and opioid use, the lack of quantitative confirmation, and the chaotic use of psychoactive substances limits the identification of specific cardiac signs related to stimulants. This clinical symptom registration was retrospective, and there is a high level of reproduction error. The study did not account for the corrected QT interval on the ECG. Left ventricular ejection fraction was assessed only by the Teicholz method, and right ventricular ejection fraction - only by TAPSE. Ventricular diastolic function has not been assessed by other methods, such as tissue Doppler.

CONCLUSION

Withdrawal syndrome from synthetic cathinones is linked to a prolonged QT interval on the ECG, in contrast to opioid withdrawal, highlighting the importance of regular QT interval monitoring to prevent serious arrhythmias. Conversely, opioid withdrawal is associated with a more pronounced reduction in left ventricular ejection fraction compared to synthetic cathinones. This suggests the need for evaluating natriuretic peptides in opioid withdrawal patients and considering treatments for chronic heart failure with preserved ejection fraction.

ACKNOWLEDGEMENT

We thank the Department of "Republic Scientific and Practical Centre for Mental Health" doctors for their contribution.

REFERENCES

1. 4 Cross-cutting issues: evoving trends and new challenges 2020. Available from: www.unodc.org/wdr2020 [cited on 9 Jul. 2024]
2. Simão AY, Antunes M, Cabral E, Oliveira P, Rosendo LM, Brinca AT, et al. An Update on the Implications of New Psychoactive Substances in Public Health. Int J Environ Res Public Health 2022; 19(8): 4869.
3. Hyde JF, Browning E, Adams R. Synthetic homologs of d,l-ephedrine. J Am Chem Soc 1928; 50(8): 2287–92.
4. Kurcevič E, Lines R. New psychoactive substances in Eurasia: a qualitative study of people who use drugs and harm reduction services in six countries. Harm Reduct J. 2020; 1;17(1):94.
5. United Nations Office on Drugs and Crime. Final act of the United nations conference for the adoption of a protocol on psychotropic substances. 2013: 71-5
6. EMCDDA–Europol Joint Report on a new psychoactive substance: 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (α-PVP) | www.emcdda.europa.eu. [cited on 9 Jul 2024]
7. Wojcieszak J, Andrzejczak D, Wojtas A, Golembiowska K, Zawilska JB. Effects of the new generation α-pyrrolidinophenones on spontaneous locomotor activities in mice, and on extracellular dopamine and serotonin levels in the mouse striatum. Forensic Toxicol 2018; 1; 36(2): 334–50.
8. Baumann MH, Ayestas MA, Partilla JS, Sink JR, Shulgin AT, Daley PF, et al. The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters in Brain Tissue. Neuropsychopharmacol 2012; 37(5): 1192.
9. Mladěnka P, Applová L, Patočka J, Marisa Costa V, Remiao F, Pourová J, et al. Comprehensive review of cardiovascular toxicity of drugs and related agents TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. Med Res Rev 2018; l; 38(4): 1332-403.
10. Beck O, Franzén L, Bäckberg M, Signell P, Helander A. Toxicity evaluation of α-pyrrolidinovalerophenone (α-PVP): results from intoxication cases within the STRIDA project. Clin Toxicol (Phila) 2016; 8; 54(7): 568–75.
11. Cherry S V., Rodriguez YF. Synthetic Stimulant Reaching Epidemic Proportions: Flakka-induced ST-elevation Myocardial Infarction With Intracardiac Thrombi. J Cardiothorac Vasc Anesth 2017 ;1; 31(1): e13–4.
12. Potocka-Banaś B, Janus T, Majdanik S, Banaś T, Dembińska T, Borowiak K. Fatal Intoxication with α-PVP, a Synthetic Cathinone Derivative. J Forensic Sci 2017; 1; 62(2):5 53–6.
13. James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, et al. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J 2011; 28(8): 686.
14. Roayaei P, Aminorroaya A, Vasheghani-Farahani A, Oraii A, Sadeghian S, Poorhosseini H, et al. Opium and cardiovascular health: A devil or an angel? Indian Heart J 2020; 1; 72(6): 482.
15. Prilutskaya M, Yussopov O, Negay N, Altynbekov K, Tokayeva M. Prevalence of new psychoactive substances addiction: a hospital-based cross-sectional study. J Clin Med Kazakhstan 2020; 15; 1(55): 11–6.
16. Prilutskaya M, Bersani FS, Corazza O, Molchanov S. Impact of synthetic cannabinoids on the duration of opioid-related withdrawal and craving among patients of addiction clinics in Kazakhstan: A prospective case–control study. Hum Psychopharmacol Clin Exp 2017; 1; 32(3): e2618.
17. Clinical protocols of the Ministry of Health of the Republic of Kazakhstan, articles on diseases - Reference system MedElement.
18. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009; 17; 53(11): 982–91.
19. Reddy PKV, Ng TMH, Oh EE, Moady G, Elkayam U. Clinical Characteristics and Management of Methamphetamine-Associated Cardiomyopathy: State-of-the-Art Review. J Am Hear Assoc Cardiovasc Cerebrovasc Dis 2020; 6; 9(11): e16704.
20. Dmochowska P, Godlewska I, Balmas J, Młynarska K, Narkun K, Zawadzki A, et al. Designers Drugs—A New Challenge to Emergency Departments—An Observational Study in Poland. Medicina (B Aires) 2020;1; 56(7): 1–13.
21. Karrari P, Mehrpour O, Afshari R, Keyler D. Pattern of illicit drug use in patients referred to addiction treatment centres in Birjand, Eastern Iran. JPMA - Journal Of Pakistan Medical Association. 2013; 63(6): 711.
22. So-Armah K, Benjamin LA, Bloomfield GS, Feinstein MJ, Hsue P, Njuguna B, et al. HIV and cardiovascular disease. lancet HIV 2020;1; 7(4): e279.
23. Papaseit E, Olesti E, Pérez-Mañá C, Torrens M, Fonseca F, Grifell M, et al. Acute Pharmacological Effects of Oral and Intranasal Mephedrone: An Observational Study in Humans. Pharmaceuticals 2021; 1; 14(2): 1–13.
24. Meng H, Cao J, Kang J, Ying X, Ji J, Reynolds W, et al. Mephedrone, a new designer drug of abuse, produces acute hemodynamic effects in the rat. Toxicol Lett 2012; 208(1): 62–8.
25. Ünübol B, Izci F, Izci S. Electrocardiographic Abnormalities During and After Withdrawal in Patients Diagnosed with Opioid Use Disorder. Arch Neuropsychiatry 2023; 60(4): 304.
26. Naserzadeh P, Jokar F, Vafaei F, Seydi E, Pourahmad J. Toxicity of new synthetic amphetamine drug mephedrone on rat heart mitochondria: A warning for its abuse. Xenobiotica 2018; 48(12): 1278–84.
27. Zwartsen A, de Korte T, Nacken P, de Lange DW, Westerink RHS, Hondebrink L. Cardiotoxicity screening of illicit drugs and new psychoactive substances (NPS) in human iPSC-derived cardiomyocytes using microelectrode array (MEA) recordings. J Mol Cell Cardiol 2019; 1; 136: 102–12.
28. Hobbs JM, Derienz RT, Baker DD, Shuttleworth MR, Pandey M. Fatal Intoxication by the Novel Cathinone 4-Fluoro-3-methyl-α-PVP. J Anal Toxicol 2022; 1; 46(3): E101–4.
29. Selcuk M, Saylik F, Mutluer FO, Yildirim E, Deniz O. Effect of heroin on right ventricular cardiac performance. Cardiovasc J Afr 2020; 1; 31(5): 241.

ORIGINAL ARTICLE

Assessing the impact of a 4-week physical training regimen on cardiorespiratory fitness among firefighter recruits

Rosnah Ismail, DrPH[1], Noor Dalila Inchi Zainal Abidin, MPH[1], Asnarulkhadi Abu Samah, PhD[2], Fathiah Jabir, MPH[1], Nor Hisham Mohammad, MBA[3], Abdul Khair Osman, MOSHRM[3], Ismail Abdul Ghani, BMgt (Hons)[3], Ashrul Riezal Asbar, BMEng[3]

[1]Department of Public Health Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia,[2]Department of Social and Development Science, Faculty of Human Ecology, Universiti Putra Malaysia, [3]Fire and Rescue Department of Malaysia

ABSTRACT

Introduction: Cardiorespiratory fitness is crucial for safe and efficient performance in executing firefighting tasks. The study aims to assess the effects of Phase 1 of a newly designed 4-week physical training regimen on changes in cardiorespiratory fitness, health parameters and other physical fitness elements. Phase 1 was crafted to primarily focus on improving firefighter recruits' cardiorespiratory fitness to prime their body for the subsequent phase of exercise.

Materials and Methods: A quasi-experimental study employing a one-group pre- and post-intervention was carried out involving 142 male firefighter recruits from a Fire and Rescue Academy in Malaysia. Various aspects of physical fitness changes, including speed, agility, and coordination (SAC), muscle strength, endurance, and power, were evaluated at baseline (Week 1) and upon completion of the first phase (Week 5). Changes in health parameters, such as blood pressure, resting heart rate, body weight, muscle mass, body fat percentage, and body mass index, were also assessed. A paired sample t-test was conducted with the significance level set at 0.05. The magnitude of changes was assessed using the following criteria: values of 0.3 were considered a small effect size, 0.5 indicated a moderate effect size, and 0.8 signified a large effect size.

Results: Upon completion of the first phase of the physical training regimen, there was a statistically significant improvement in cardiorespiratory fitness, with a mean increment of VO2max was 9 mL/kg/min (95% CI: 8.33, 9.58, p<0.001, large effect size of 2.40). Both pre-and post-intervention assessments of abdominal and upper body muscle strength and endurance showed statistically significant improvement with the mean difference of 11 sit-ups (95%CI: 10.08, 12.01; p<0.001, large effect size of 1.89) and 1.5 pull-ups (95%CI: 1.07, 1.86; p<0.001, moderate effect size of 0.63), respectively. Health parameters showed similar, except for systolic BP (SBP). There was a small increment in recruits' SBP following the 4-week training period with a mean difference of 4.3 mmHg (95%CI: 2.37, 6.24; effect size = 0.37, p<0.001).

Conclusion: The first phase of the newly introduced four-week physical training regimen has proven effective in enhancing cardiorespiratory fitness, as well as abdominal and upper body muscle strength and endurance. Additionally, the regimen has positively influenced several health parameters, except for systolic blood pressure. The observed increase in average systolic blood pressure indicates a necessity for continuous monitoring at the academy to address this issue effectively.
confirm our findings.

KEYWORDS:
Firefighters, physical fitness, cardiorespiratory fitness

INTRODUCTION

Firefighting is a high-risk profession that frequently exposes firefighters to hazardous and life-threatening situations. Therefore, maintaining optimal health and physical fitness is paramount for ensuring firefighters able to fulfil their duties safely and effectively.[1] Firefighters are required to be aerobically fit and have good total body strength and local muscular endurance to carry heavy equipment, climb stairs, carry out victims and move quickly while donning heavy protective gear. Given the physically demanding nature of firefighting, maintaining good physical fitness is instrumental in preventing musculoskeletal injuries and enhancing overall job performance.[1,2] Regular physical training is essential in achieving and sustaining this level of fitness.[3] Additionally, physical fitness training offers significant health benefits, including a reduced risk of heart disease and other chronic illnesses.[4]

Despite the imperative for firefighters to uphold optimal health and physical fitness, concerns persist regarding their current fitness status among stakeholders. Research indicates that firefighters may not engage in adequate physical activity and often lack the requisite fitness levels necessary for safe and efficient job performance.[5] In Malaysia, active firefighters are mandated to undergo the Individual Physical Proficiency Test (IPPT), a biannual physical fitness assessment.[6] However, despite these measures, the health parameters and physical fitness levels of firefighters in Malaysia remain, relatively, below the expected standard.[7] To address these concerns, the National Fire Protection Agency (NFPA) has established a set of health and fitness standards essential for executing 14 essential job tasks effectively.[8] Therefore, several guidelines have been established in western countries to implement structured

This article was accepted: 08 October 2024
Corresponding Author: Fathiah Jabir
Email: fathiahjabir@gmail.com; p137734@siswa.ukm.edu.my

physical training and fitness programs within fire academies and fire stations aiming to enhance and sustain firefighters' fitness levels.[9,10] One notable guideline is The Fire Service Joint Labor Management Wellness-Fitness Initiative (WFI), which has been integrated as a training program in selected firefighter academies in the United States.[10] Research indicates its effectiveness in improving the health and physical fitness of firefighter recruits.[11] In contrast, within the local context, there is a lack of documented guidelines for guiding the development of training regimens for firefighters. Consequently, the current physical training regimen lacks standardisation in its implementation and exhibits variability in practices, primarily driven by the individual preferences of physical training instructors at the Fire and Rescue Academy. This variance in training may result in significant differences in the health and physical fitness levels of recruits across different platoons during the 18-week firefighting training period. To address this issue, a four-phase physical training module has been developed, aiming to provide a standardized and structured physical training regimen. This training is administered under the supervision of trained and certified physical trainers at the academy.

Before proceeding with the implementation of subsequent phases (Phases 2 to 4) of the newly developed module, this study aimed to assess the effectiveness of a brief 4-week period of Phase 1 of the physical training regimen. Phase 1 of the module primarily focused on improving recruits' cardiorespiratory fitness, also term as aerobic or cardiovascular fitness, which refers to the functional capacity of an individual's lungs, heart, and blood vessels to deliver oxygen-riched blood to active muscles for consumption during sustained physical activity.[12] This was evaluated by measuring the completion time for a 2.4 km run, serving as one of the indicators for cardiorespiratory fitness status ascertainment. Additionally, this study examined changes in recruits' health parameters (such as blood pressure (BP), resting heart rate (RHR), body weight (BW), muscle mass (MM), body fat percentage (BF%), and body mass index (BMI)) and other physical fitness parameters (including speed, agility, and coordination (SAC), as well as muscle strength, endurance, and power).

MATERIALS AND METHODS

Study Design and Participants

This study utilized a quasi-experimental design with a one-group pre- and post-intervention method involving firefighter recruits. A convenient sampling method was employed, enrolling all male firefighter recruits (n=145) who joined the East Region Fire and Rescue Academy Malaysia on 1 February 2023. The initial enrolment exceeded the minimum predetermined sample size of 34 and was calculated using G*Power Version 3.1.9.7 for testing the mean difference between two dependent means of matched pairs. The calculation was based on an alpha error probability of 0.05, a study power of 0.80, and a hypothetical moderate effect size of 0.5.13 No female recruits were part of the intake. Before joining the academy, all recruits underwent pre-employment medical examinations and were certified medically fit by the attending medical officers.

The Physical Training Module

The new physical training module consists of four phases, implemented on a 6-day weekly schedule. The preliminary framework was developed by a panel of six experts, comprising three certified physical training instructors (PTIs) and three physical trainers (PT), the module was refined through a series of modified and extended Nominal Group Techniques (NGTs) from 19 to 23 June 2022. The modified NGT identified the three top-ranking exercises for functional strength required by firefighter recruits, including pushing, pulling, lifting, carrying, and dragging, as described elsewhere.[14]

The extended NGT represented a continuation of the effort to create a structured 6-day physical training regimen, building upon gathered insights from prior iterations of modified NGTs. They were tasked with crafting a daily physical training regimen starting on Saturday and ending on Thursday. The regimen should encompass the following aspects of functional fitness: 1) core strength exercises, 2) cardiovascular training sessions, 3) functional movements involving pushing, pulling, and carrying, 4) lower body exercises, combined with lifting, carrying, and dragging exercises, and 5) total body exercise incorporating core strength, cardiovascular endurance, flexibility, pushing, pulling, carrying, lifting, and dragging, to be included in the regimen at least once a week. They were reminded to incorporate dynamic stretching into warm-up and static stretching into cool-down routine. As a result of the extended NGT process, a daily exercise regimen was formulated, comprising a sequence of exercises tailored to individual repetition maximums and corresponding rest interval time.
Subsequently, the validation process was carried out by a panel of subject matter experts, comprising 5 certified PTIs, possessing equivalent experience and expertise to the previous module developers, alongside two senior firefighters. The validation process occurred from 29th November to 1st December 2022, with a focus on assessing the feasibility of the physical training regimen for firefighter recruits. Both the development and validation processes were moderated by a Public Health Medicine Specialist, supported by a senior firefighter officer from the Special Tactical Operation and Rescue Team of Malaysia, and aided by a doctoral student. Taking into account the feedback from the expert group during the validation process, the physical training regimen was expanded to four phases: beginner, also termed as Phase 1 (4 weeks), intermediate (8 weeks), final (4 weeks), and transition (2 weeks). Each phase of the module focuses on different aspects of physical fitness with a structured and standardised physical training regimen. The Phase 1, spanning four weeks, emphasizes the enhancement of recruits' cardiorespiratory fitness (Table I). During the initial two weeks of the training period, the majority of the training time was dedicated to aerobic exercises, with the remainder allocated to muscle-strengthening exercises. In the subsequent two weeks, equal time was allotted for both aerobic and muscle-strengthening exercises.

Table I outlines several types of aerobic activities combined with muscle-strengthening exercise variants (from regression to progression version) for muscle groups of legs, core of body, chest, and arms. On the one hand, several types of runs can attain moderate-intensity aerobic exercise, generally

Table I: Phase 1 of Physical Training Module Outline

Physical Training Regimen	Week 1	Week 2	Week 3	Week 4
Run (Long slow distance – with a pace that recruits can sing, Fartlek, circuit, interval run, tempo run), % of time	60	60	50	50
Muscle-strengthening exercise, % of time	40	40	50	50

Workout Time

Warm up: 15 mins, Training phase: 35 minutes, Cool down: 10 minutes

List of Muscle-Strengthening Exercise

Total Body Exercise	Upper Body Exercise	Core Body Exercise	Lower Body Exercise
• Burpee • Jumping jack • Star jump • Mountain climbers	• Push-up • Wide push-up • Diamond push-up • Full/elbow plank • Plank side • Plank arm/leg raise • Pike push-up • Shoulder taps • Arm scissor • Supine push-up • Downward-facing to upward-facing	• Superman • Single leg bridge • Sit-up • Crunch • Bike crunch • Sitting twist • Raise leg hold • Flutter kicks • Windshield wipers • Knee to elbow • V-ups • L-shape lifting	• Forward lunges • Jump lunges • Side lunges • Reverse lunges • Front & back lunges • Squat • Squat and jump • Sumo squat • Calf raise • Side-to-side shuffle • High knees

Table II: Health and physical fitness parameters of recruits at Week 1 and Week 5.

Variables	Week 1 Mean (SD)	Week 5 Mean (SD)	Mean Difference (95% CI)	t-statistics (df)	p-value	Effect size (d)
Health Parameters						
Systolic BP, mmHg	120.8 (13.04)	124.4 (11.16)	4.3 (2.37, 6.24)	4.4 (141)	<0.001*	0.37
Diastolic BP, mmHg	76.2 (9.18)	71.1 (7.67)	-5.2 (-6.65, -3.67)	6.9 (141)	<0.001*	0.58
Resting heart rate, bpm	86.9 (18.4)	68.6 (12.04)	-18.3 (-20.86, -15.78)	14.3 (141)	<0.001*	1.20
Body weight, kg	68.2 (9.26)	65.8 (7.02)	-2.3 (-2.87, -1.79)	8.6 (141)	<0.001*	0.71
Body Fat Percentage, %	16.2 (4.69)	12.8 (3.00)	-3.4 (-3.79, -2.97)	16.5 (141)	<0.001*	1.37
Body muscle mass, kg	54.0 (5.23)	54.4 (4.78)	0.4 (0.16, 0.64)	3.3 (141)	0.001*	0.28
BMI, kg/m^2	24.5 (3.00)	23.6 (2.19)	-0.8 (-1.02, -0.64)	8.6 (141)	<0.001*	0.70
Physical Fitness Parameters						
Speed, Agility, and Coordination:						
SR completion time, second	10.48 (0.67)	10.52 (0.88)	0.03 (0.08, 0.14)	0.6 (141)	0.531	0.04
Lower body explosive muscle power:						
SBJ distance, cm	206.0 (26.00)	206.3 (23.07)	0.3 (3.20, 3.72)	0.1 (141)	0.882	0.01
Abdominal muscle strength and endurance:						
SU, n number per minute	35.2 (7.28)	46.2 (5.51)	11.0 (10.08, 12.01)	22.6 (141)	<0.001*	1.89
Upper body muscle strength and endurance:						
PU, n maximum number	5.3 (3.39)	6.8 (3.32)	1.5 (1.07, 1.86)	7.3 (141)	<0.001*	0.63
Cardiorespiratory fitness:						
2.4km run time, minute	13.2 (2.05)	10.6 (1.41)	-2.6 (-2.87, -2.42)	23.3 (141)	<0.001*	1.92
Estimated VO_2max, mL/kg/min	40.9 (5.93)	49.9 (5.60)	9.0 (8.33, 9.58)	28.5 (141)	<0.001*	2.40

*p<0.05

Abbreviations: PU= pull up, SBJ= Standing Broad Jump, SR=Shuttle run, SU= Bent-knee sit-up

targeting for 65 to 75 per cent of the maximum heart rate. On the other hand, the chosen muscle-strengthening exercise involves multi-joint movements that effectively target the major muscle groups resulting in a perceived exertion rating ranging from level 3 (indicating moderate effort i.e. 65% effort) to level 4 (reflecting somewhat hard effort i.e. 70% effort).[15] This also aligns with achieving moderate-intensity aerobic exercise for recruits. The specified exercises are easily monitored to attain the moderate level of intensity recommended by the American College of Sports Medicine.16 Additionally, firefighters familiar with these exercises as they are a regular workout regimen.

The recruits' physical training sessions typically occurred in the morning and afternoon from Saturday to Thursday, each lasting an hour. The recruits were divided into 5 platoons. Each was supervised by four to five PTs trained in implementing this module, overseen by three PTIs. The PTs were given the flexibility to select the type of muscle-strengthening exercise to incorporate into the run. The PTs underwent training sessions from 12th to 15th December 2022, and from 29th to 31st January 2023 to ensure standardization in delivering the program.

Data Collection
Before data collection, the recruits received a short briefing regarding the purpose and scope of the study, and their informed consent was obtained. Authorization for the use of the health and physical fitness data was granted by the Planning and Research Division of FDRM. Ethical approval for the study was obtained from the Ethical Committee Board of The National University of Malaysia (Code: FF-2023-185). Baseline data for various health parameters and physical fitness were collected during week 1, while post-intervention data were collected on the first day of week 5. Data collection for health parameters during both weeks occurred one day before the physical fitness test. Recruits were instructed to wear standard sports attire, comprising a short-sleeved white t-shirt, sports pants, and sports shoes.

Health Parameters
Height: Recruits' height was measured in metres using a portable stature meter to the nearest 0.01 m without wearing shoes in standing position and their back against the wall. Their height was mark at the level of head vertex. The distance from the floor to the mark was measured.

Systolic BP (SBP), Diastolic BP (DBP) and Resting Heart Rate (RHR): SBP (mmHg), DBP (mmHg) and RHR (beats per min, BPM) were taken as described using Innomed X1 Digital Blood Pressure Monitoring.[17] Recruits were instructed to sit on a chair with a backrest for a minimum of five minutes while in a relaxed state and refrained from speaking before measurements were taken.

Body Weight (BW), Body Muscle Mass (MM), and Body Fat Percentage (BF%): BW (kg), MM (kg) and BF% were measured using a bioelectrical impedance analysis machine, the Tanita Body Fat Analyser Model 701-BC554 (Tanita Corp., Tokyo, Japan). All measurements were conducted with recruits barefoot and empty pockets. Body weight and muscle mass were measured to the nearest 0.1 kg. Recruits who experienced a reduction in body weight of more than 3% at week 5 compared to week 1 were categorized as weight loss. Those with a body weight within 3% of the initial weight difference were considered to have stable weight, while recruits who gained more than 3% weight from the baseline were categorized as weight gain.[18]

Body Mass Index (BMI): BMI (kg/m^2) was calculated during analysis as body weight in kilograms divided by height in square meters.

Physical Fitness Parameters
Recruits' physical fitness was measured using five elements of the Individual Physical Proficiency Test (IPTT).[6] The IPPT was administered in the following sequence: shuttle run, standing broad jump, bent-knee sit-up, pull-up, and concluding with the 2.4 km run.

Shuttle Run 4 X 10m (SR): This test evaluates speed, agility, and partly motor skill coordination (SAC).[19] SR measures the ability to accelerate, decelerate, change direction and explode again to an individual top speed while maintaining excellent body control. The test involved placing two small brown tissue paper roll core tubes, each measuring 45mm in diameter x 100mm in height x 1mm in thickness, as line markers at a distance of 10 meters apart. The test required recruits to run back and forth between the two markers in four repetitions, covering a total shuttle run distance of 40 meters (4x10m), as quickly as possible. Additionally, recruits are required to pick up the paper roll core tubes as they turn to sprint back to the starting point. The duration for completing the entire circuit was measured to the nearest 0.01 second.

Standing Broad Jump (SBJ): This test evaluates the explosive muscle power of the lower limbs. It was a two-footed horizontal jump from a standing position at a line on the ground with their feet slightly apart. The distance between the starting line and the recruit's heels was measured to the nearest centimetre.

Bent-knee sit-up (SU): The SU test assesses the abdominal muscle strength and endurance of recruits. During the test, recruits laid flat with knees bent and feet firmly planted on the ground, while hands were positioned behind the earlobes. The recruit's partner held their feet securely. A sit-up was deemed complete when the recruit's elbows touched their knees and their back returned to the ground afterwards. The number of sit-ups performed by recruits within a minute was recorded.

Pull-up (PU): The PU test evaluates the upper body muscle strength and endurance of recruits. Recruits were required to grasp an overhead bar using a pronated grip, with arms fully extended. They then lifted their body until their chin was above the bar, before returning to the initial position with arms fully extended. The movement should be executed smoothly, without jerky motions, swinging the body, or kicking or bending the legs. The maximum number of complete PUs performed by recruits was recorded.

Cardiorespiratory fitness assessment using 2.4 km run time: The recruits were required to complete the run in the shortest time possible. The time taken to complete the 2.4km was measured to the nearest seconds. The estimated VO_2 max (Est. VO_2 Max) was calculated by using the following formula, based on the previous study.[20]

VO_2 max = (483 / run time in minutes) + 3.5

VO_2 max, or maximal oxygen uptake, is a measure of the maximum amount of oxygen that an individual can utilize during intense exercise. It is typically expressed as millilitres of oxygen per kilogram of body weight per minute (ml/kg/min). The value of VO_2 max is considered one of the best indicators of cardiorespiratory fitness, also termed, aerobic fitness and endurance capacity.[21]

Data Analysis
The data were analysed using IBM SPSS version 27. Before analysis, all data were checked for normality using histogram and Q-Q Plot, skewness (-1 and +1) and kurtosis (-1 and +1). Descriptive analysis was performed and reported for all variables at week 1 and week 5. Following descriptive analysis, a paired samples t-test was conducted to determine

the effect of a 4-week physical training regimen on health and physical fitness parameters with the significance level set at 0.05. Effect sizes were also reported to determine the strength of the difference between pre and post-intervention. The d effect sizes were interpreted as small (d = 0.2), moderate (d = 0.5) and large (d = 0.8).[23]

RESULTS

A total of 145 firefighter recruits were recruited for this study in week 1. Three recruits withdrew from the academy thus, were excluded from this study, leaving a final sample size of 142 firefighter recruits in week 5. Their mean age and height were 27 years old (SD=3.36) and 1.67m (SD=0.05), respectively. The descriptive analysis (mean and SD), results of bivariate analysis (paired t-test), and the effect size are presented in Table II.

Health Parameters

Results of comparison between pre and post-intervention for all parameters revealed statistically significant differences between before and after Phase 1 of the new module. All health parameters, except systolic blood pressure and MM, significantly decreased at week 5 in comparison to week 1. Furthermore, large effect sizes were observed for RHR and BF%. The BF% showed the highest effect size and MM had the lowest. Among recruits, 53.5% experienced weight loss, 35.9% maintained stable weight, and 10.6% showed weight gain.

Physical Fitness Parameters

Analysis of comparison for physical fitness parameters revealed significant changes between pre-and post-intervention for cardiorespiratory fitness, abdominal and upper body muscle strength and endurance. All three parameters increased significantly at week 5. The effect size for all significant parameters showed large effect sizes, except for PU, which has a moderate effect size of 0.63. As expected, both STR and SBJ had no significant improvement at week 5.

DISCUSSION

This quasi-experimental study aimed to assess the impact of a 4-week physical training regimen on cardiorespiratory fitness, along with various health and physical fitness parameters. The findings revealed significant changes induced by the physical training regimen across most health and fitness parameters, particularly in cardiorespiratory fitness. Contrary to our expectations, the SBP readings increased instead of decreasing. However, DBP and RHR demonstrated a significant reduction, consistent with findings from previous meta-analysis.[22] These changes were probably due to acute physiological adaptation as a result of aerobic training, which affects parasympathetic and sympathetic nervous activity, nitric oxide, the prostanoid system, the renin-angiotensin system, and vascular remodeling.[23] The unexpected rise in mean systolic blood pressure contrasts with expectations, given that aerobic training typically lowers vascular resistance through shear stress on the vascular wall. Aerobic exercise also triggers the release of growth factors and exerkines from skeletal muscles and organs, resulting in decreased vascular systolic blood pressure.[24] Previous studies have demonstrated the association between higher physical activity and fitness with lower blood pressure.[25] Although it has been shown that SBP increases with submaximal exercise workload, they are typically transient and would normalise during the recovery phase.[26] As recruits' blood pressure was measured after adequate rest in this study, the increase in blood pressure may be due to other factors that were not assessed in this study, such as psychosocial stress,[27] that may arise from the firefighting training itself, as demonstrated in previous study.[28] This demonstrates that the implementation of some interventions, such as blood pressure monitoring, may be necessary for recruits at the academy, as firefighters with elevated blood pressure are at higher risk of late onset hypertension and cardiovascular events.[29,30]

Consistent with previous findings,[31] BW, BMI, and BF% showed significant reduction while MM significantly increased. The reduction in BW, BMI and BF% can occur when an individual has a negative energy balance, which is when energy expenditure exceeds energy intake, and regular exercise causes increased energy expenditure when carried out regularly.[32] Regular aerobic exercise with the inclusion of a total body exercise has the effect of increasing muscle mass by causing muscle hypertrophy, which has been observed to occur in a short period of two weeks after initiation of training.[33,34] This causes an increase in muscle mass and would explain why some recruits had stable weight or weight gain. Furthermore, prolonged exercise leads to a decrease in body fat from the increase in lipolysis and fat oxidation.[35]

In this study, SAC and explosive power of the lower limbs showed no significant difference. These findings could be attributed to the design of Phase 1 of the physical training regimen which prioritized enhancing recruits' cardiorespiratory fitness rather than focusing on building lower body endurence and power. Phase 1 was crafted to prime cardiorespiratory fitness before progressing to Phase 2, an eight-week physical training regimen, focusing on developing muscle strength, endurance, and power of upper, middle and lower body muscle groups. High SAC can indeed aid firefighters in navigating the fire ground more effectively, especially during unpredictable and unforeseen circumstances.[36] By possessing enhanced SAC, firefighters can move with greater agility and efficiency, allowing them to respond quickly and adapt to changing conditions. This ability is crucial for firefighters as they manoeuvre through potentially hazardous environments, enabling them to better execute tasks and respond to emergencies effectively.[37]

The results indicate significant enhancement in both abdominal and upper body muscle strength and endurance when comparing week 5 measurements to the baseline at week 1, consistent with findings from previous studies incorporating aerobic and muscle-strengthening exercise programs.[31,37] Despite the primary focus of the initial phase to enhance cardiorespiratory fitness, the integration of total body exercises for muscle strengthening led to notable improvements in muscle strength and endurance of the upper body and abdominal core muscles. These improvements were evident even with once-per-week training sessions targeting specific muscle groups.[38] This phenomenon

holds particular significance for untrained individuals, where rapid advancements in muscle fitness are largely attributed to neural muscle adaptation, a process likely facilitated by increased training frequency.[39]

This study reveals that by week 5, the average estimation of VO2 max significantly surpasses the recommended cardiorespiratory standard of 42 mL/kg/min outlined by NFPA.[8] Continuous exercise has been shown to enhance VO_2 max by increasing skeletal muscle mitochondrial content, myoglobin desaturation, and oxidative capacity.[40] Achieving this level of fitness equips firefighters to execute their duties safely while donning full firefighting gear and breathing apparatus, and it also serves as a protective factor against cardiovascular events.[1] Cardiorespiratory fitness is directly associated with the capacity to sustain dynamic, moderate-to-vigorous exercise involving large muscle groups.[21] Given the physically demanding nature of firefighting tasks, which place considerable strain on the cardiovascular system, maintaining optimal cardiorespiratory fitness is paramount. Enhancing cardiorespiratory fitness enhances firefighters' ability to perform tasks that demand sustained cardiorespiratory effort. Therefore, the decision to prioritize the improvement of cardiorespiratory fitness during the initial phase of training is justified.

This study demonstrates that significant improvements in the health and fitness parameters of firefighter recruits can be achieved within a 4-week physical training regimen utilizing only person's bodyweight. Therefore, recruits can promptly commence exercising and seamlessly integrate it into their daily routines. Given the stringent selection process for firefighters, including thorough medical and physical screenings prior to academy acceptance, potential confounding factors such as underlying medical conditions were minimized. Furthermore, recruits in the academy adhere to a structured full-day schedule, reside in on-site accommodation provided by the academy, and receive standardized meals throughout the training period. These controlled settings effectively limit the impact of external physical activities and variations in nutritional intake on the study outcomes.

This study is subject to several limitations. Firstly, control group was not employed due to ethical and practical concerns. Withholding training from recruits could be perceived as unethical, considering the necessity to sufficiently equip them for the challenges of firefighting responsibilities. Secondly, the absence of female recruits in this study is notable. Future research should aim to include female firefighters, as training adaptations and outcomes may differ between genders. Lastly, the study was conducted in only one out of five academies in Malaysia due to technical constraints limiting the generalizability of the findings to the entire country. These limitations underscore the need for caution when interpreting and applying the study's results.

CONCLUSION

The initial phase of the newly implemented four-week physical training regimen has demonstrated success in improving cardiorespiratory fitness, abdominal, and upper body muscular strength and endurance. Additionally, the regimen has shown a significant impact on various health parameters, except systolic blood pressure. The observed increase in average systolic blood pressure indicates a necessity for continuous monitoring and implementation of intervention measures at the academy to address this issue effectively. This study also highlights that improvement in physical fitness can be achieved even with minimal equipment and cost. The module's effectiveness in improving body composition and physical fitness measurements sets a strong foundation for the subsequent phases, which are likely to build upon these improvements. Future studies should seek to replicate the findings in other Fire and Rescue Academies to gain a thorough knowledge of the module's efficacy and adaptability in various settings and larger samples.

ACKNOWLEDGEMENTS

We gratefully acknowledge the valuable contributions of Fire and Rescue Department of Malaysia for their availability of resources and guidance to ensure the evaluation of this physical training regimen is fruitful. The author thanks to all physical training instructors and physical trainers who directly or indirectly employed the 4-week physical training regimen. The study received minimal funding from the Faculty of Medicine Fundamental Grant, National University of Malaysia.

REFERENCES

1. Ras J, Kengne AP, Smith DL, Soteriades ES, November R V, Leach L. Effects of Cardiovascular Disease Risk Factors, Musculoskeletal Health, and Physical Fitness on Occupational Performance in Firefighters-A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2022;19(19): 11946.
2. Ras J, Soteriades ES, Smith DL, Kengne AP, Leach L. Association between physical fitness and musculoskeletal health in firefighters. Front Physiol 2023; 14: 1210107.
3. Cornell DJ, Gnacinski SL, Meyer BB, Ebersole KT. Changes in Health and Fitness in Firefighter Recruits. Med Sci Sport Exerc 2017; 49(11): 2223–33.
4. Gendron P, Lajoie C, Laurencelle L, Lemoyne J, Trudeau F. Physical training in the fire station and firefighters' cardiovascular health. Occup Med (Chic Ill) 2020; 70(4): 224–30.
5. Storer TW, Dolezal BA, Abrazado ML, Smith DL, Batalin MA, Tseng CH, et al. Firefighter Health and Fitness Assessment. J Strength Cond Res 2014; 28(3): 661–71.
6. Fire and Rescue Department Malaysia. Standing Order of the Director General Number 2 of 2014: Implementation of the Individual Physical Proficiency Test (IPPT). Fire and Rescue Department Malaysia 2014. [cited July 2023]. Available from: https://www.bomba.gov.my/wp-content/uploads/2021/07/ippt.pdf
7. Atikah CW, Nihayah M, Leonard JH, Omar B, Noor Ibrahim MS, Zurkarnain MK, et al. A cross-sectional evaluation on physical fitness of Malaysian firefighters. Sains Malaysiana 2015; 44(10): 1461–6.
8. National Fire Protection Association. 2022. NFPA code 1582: Standard on Comprehensive Occupational Medical Program for Fire Departments US. [cited July 2023]. Available from: https://www.nfpa.org/codes-and-standards/nfpa-1582-standard-development/1582
9. Nottinghamshire Fire and Rescue Service. Firefighter Recruitment Fitness Guidance: Yes You Can [cited June 2023]. Available from: https://www.notts-fire.gov.uk/media/p52at3z4/firefighter-recruitment-fitness-guidance.pdf

10. International Association of Fire Fighters, International Association of Fire Chiefs. 2018. The Fire Service Joint Labor Management Wellness-Fitness Initiative. 4th Edition. [cited June 2023]. Available from: https://www.iafc.org/docs/default-source/1safehealthshs/wfi-manual.pdf
11. Lockie RG, Dulla JM, Higuera D, Ross KA, Orr RM, Dawes JJ, et al. Body Composition and Fitness Characteristics of Firefighters Participating in a Health and Wellness Program: Relationships and Descriptive Data. Int J Environ Res Public Health 2022; 19(23): 15758.
12. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation 2016; 134(24): e653–99.
13. Beck TW. The importance of a priori sample size estimation in strength and conditioning research. J Strength Cond Res 2013; 27(8): 2323–37.
14. Ismail R, Abu Samah A, Zainal Abidin NDI, Mohammad NH, Osman AK, Abdul Ghani I, et al. Development of Physical Training Program to Boost Functional Strength in Firefighter Recruits Using a Modified Nominal Group Technique. Preprint. 2024. [cited April 2024]. Available from: https://www.researchsquare.com/article/rs-3831653/v1
15. Arney BE, Glover R, Fusco A, Cortis C, de Koning JJ, van Erp T, et al. Comparison of RPE (Rating of Perceived Exertion) Scales for Session RPE. Int J Sports Physiol Perform 2019; 14(7): 994–6.
16. Zuhl M. Tips for Monitoring Aerobic Exercise Intensity. American College of Sport Medicine 2020 [cited July 2023]. Available from: https://www.acsm.org/docs/default-source/files-for-resource-library/exercise-intensity-infographic.pdf
17. American Heart Association. Monitoring Your Blood Pressure at Home. American Heart Association 2023 [cited April 2024]. Available from: https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings/monitoring-your-blood-pressure-at-home
18. Mathias KC, Bode ED, Stewart DF, Smith DL. Changes in Firefighter Weight and Cardiovascular Disease Risk Factors over Five Years. Med Sci Sports Exerc 2020; 52(11): 2476–82.
19. Kolimechkov S, Petrov L, Alexandrova A. Alpha-Fit Test Battery norms for children and adolescents from 5 to 18 years of age obtained by a linear interpolation of existing European physical fitness references. Eur J Phys Educ Sport Sci 2019; 5(4): 1–14.
20. Fahey T, Insel P, Roth W. 2007. Fit & Well: Core Concepts and Labs in Physical Fitness and Wellness. 7th Edition. McGraw-Hill.
21. American College of Sports Medicine. 2022. ACSM's Guidelines for Exercise Testing and Prescription. 11th ed. Liguori G, Feito Y, Fountaine C, Roy BA, editors. Philadelphia: Wolters Kluwer.
22. Carpio-Rivera E, Moncada-Jiménez J, Salazar-Rojas W, Solera-Herrera A. Acute Effects of Exercise on Blood Pressure: A Meta-Analytic Investigation. Arq Bras Cardiol 2016; 106(5): 422.
23. Farrell C, DR. T. Normal Versus Chronic Adaptations to Aerobic Exercise. StatPearls Publishing 2023 [cited June 2023]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572066/
24. Königstein K, Dipla K, Zafeiridis A. Training the Vessels: Molecular and Clinical Effects of Exercise on Vascular Health—A Narrative Review. Cells 2023; 12(21): 2544.
25. Bakker EA, Sui X, Brellenthin AG, Lee DC. Physical activity and fitness for the prevention of hypertension. Curr Opin Cardiol 2018; 33(4): 394–401.
26. Lee J, Vasan RS, Xanthakis V. Association of Blood Pressure Responses to Submaximal Exercise in Midlife With the Incidence of Cardiovascular Outcomes and All-Cause Mortality: The Framingham Heart Study. J Am Heart Assoc 2020; 9(11): e015554.
27. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens 2015; 28(11): 1295–302.
28. Lan FY, Yiannakou I, Scheibler C, Hershey MS, Cabrera JLR, Gaviola GC, et al. The Effects of Fire Academy Training and Probationary Firefighter Status on Select Basic Health and Fitness Measurements. Med Sci Sports Exerc 2021; 53(4): 740–8.
29. Yzaguirre I, Grazioli G, Domenech M, Vinuesa A, Pi R, Gutierrez J, et al. Exaggerated blood pressure response to exercise and late-onset hypertension in young adults. Blood Press Monit 2017; 22(6): 339–44.
30. Noh J, Lee CJ, Hyun DS, Kim W, Kim MJ, Park KS, et al. Blood pressure and the risk of major adverse cardiovascular events among firefighters. J Hypertens 2020; 38(5): 850–7.
31. Stone BL, Alvar BA, Orr RM, Lockie RG, Johnson QR, Goatcher J, et al. Impact of an 11-Week Strength and Conditioning Program on Firefighter Trainee Fitness. Sustainability 2020; 12(16): 6541.
32. Balfour J, Boster J. Physical Activity and Weight Loss Maintenance. StatPearls Publishing 2023 [cited July 2023]. Available from: https://pubmed.ncbi.nlm.nih.gov/34283417/
33. Konopka AR, Harber MP. Skeletal Muscle Hypertrophy After Aerobic Exercise Training. Exerc Sport Sci Rev 2014; 42(2): 53–61.
34. Hughes DC, Ellefsen S, Baar K. Adaptations to Endurance and Strength Training. Cold Spring Harb Perspect Med 2018; 8(6): a029769.
35. Stroh AM, Stanford KI. Exercise-induced regulation of adipose tissue. Curr Opin Genet Dev 2023; 81: 102058.
36. Lockie RG, Orr RM, Montes F, Dawes JJ. Change-of-Direction Speed in Firefighter Trainees: Fitness Relationships and Implications for Occupational Performance. J Hum Kinet 2023; 87: 225.
37. Rasteiro A, Santos V, Massuça LM. Physical Training Programs for Tactical Populations: Brief Systematic Review. Healthcare (Basel) 2023; 11(7): 967.
38. Grgic J, Schoenfeld BJ, Latella C. Resistance training frequency and skeletal muscle hypertrophy: A review of available evidence. J Sci Med Sport 2019; 22(3): 361–70.
39. Peterson MD, Rhea MR, Alvar BA. Applications of the dose-response for muscular strength development: a review of meta-analytic efficacy and reliability for designing training prescription. J Strength Cond Res 2005; 19(4): 950–8.
40. Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Front Cardiovasc Med 2019; 6: 69.

The impact of oral multinutrient supplementation on in vitro fertilisation or intracytoplasmic sperm injection outcomes: A prospective controlled study

Gopinath Muruti, MMed[1], Siti Khadijah Idris, MSc[1], Ruhaima Ramli, MPhil[1], Nuguelis Razali, MMed[1,2], Mukhri Hamdan, PhD[1,2]

[1]UMFertility, University Malaya Medical Centre, Kuala Lumpur, Malaysia, [2]Department of Obstetrics and Gynaecology, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Micronutrients influence female fertility, thus adequate levels are important for oocyte quality, maturation, fertilisation and implantation. This study prospectively evaluated the impact of oral multinutrient supplementation on fertility outcomes in In vitro fertilisation or Intracytoplasmic sperm injection (IVF/ICSI).

Materials and Methods: This was a pilot study of N=50 women, who were planning for IVF treatment in University Malaya Medical Centre, Kuala Lumpur, Malaysia from July to December 2023. Women without prior nutritional treatment were consented and assigned to either the multinutrient supplementation (Omega 3, coenzyme Q10, folic acid, selenium, vitamin E, catechins) as the study group or 5mg folic acid daily as control group for at least a month prior to their IVF treatment. All women were treated using an antagonist protocol and ovarian stimulation was started with 200 –300IU of urinary HMG and or recombinant FSH. Antagonists (Ganirelix) commenced when the leading follicle reached a diameter of 11 mm. Triggering with hCG or GnRH agonist when at least 3 follicles of 17 mm in diameter were achieved. Oocyte retrieval was performed 36th hour after trigger. Conventional IVF/ICSI was used for fertilisation. All parameters recorded and analysed using SPSS.

Results: The mean age (36.44 ± 3.33 vs 35.32 ± 3.47 years) and body mass index (25.28 ± 4.12 vs 24.80 ± 4.36 kg/m2) of women in multinutrient supplementation group was similar to control group. The Follicular Output Rate (FORT) in women on multinutrient supplementation showed a trend towards benefit compared to control group, although it is not statistically significant (68.12 ± 19.47 vs 64.91 ± 20.06, p=0.493). The mean number of MII oocytes retrieved from mature follicles and number of good quality embryo on day 3 after fertilisation were not statistically significant between the two groups (6.65 ±3.84 vs 6.09 ± 3.01, p=0.626 and 4.00 ± 3.10 vs 3.45 ± 2.30, p=0.549, respectively). In addition, there were no differences in endometrial thickness before embryo transfer in both groups (10.35 ± 1.32mm vs 10.36 ± 2.04mm, p=0.320). However, the total dose of follicle stimulating hormone and duration of controlled ovarian stimulation were lower in the study group compared to control group (2410 ± 656.82 IU vs 2706.82 ± 536.15 IU, p= 0.119 and 8.90 ± 2.13 days vs 9.68 ± 1.29 days, p=0.164, respectively).

Conclusion: A multinutrient supplementation given for a minimum of 28 days, may have a positive effect on FORT and lower use of gonadotropin. More and larger sample research is warranted to prove this effect.

KEYWORDS:
Multinutrient, Female fertility, Follicular Output Rate (FORT), In vitro Fertilisation, Intracytoplasmic Sperm Injection, Endometriosis

INTRODUCTION

Subfertility among Malaysian has recently gained the national authority attention with the decline of total fertility rate reported to came down to below replacement level.[1] Similar to many countries, many women delay conception to acquire higher education, pursuing a career, achieving financial stability and plan for late marriage.[1-3] Due to these circumstances, many women were aged with reduced ovarian reserve when they decide to conceive.[4-6] Approximately 70% of couples have no identified cause which diverted the solution to restoring potentially modifiable risk factors such as micronutrient status that may have an impact on female fertility.[7-8] Essential vitamins and minerals have important roles in the physiological processes and therefore adequate levels are important for oocyte quality, maturation, fertilisation and implantation whereas antioxidants are vital to reduce oxidative stress, a process known to impair fertility.[9] Lower recommended micronutrients levels have been reported in sub fertile women.[10-11] A similar scenario has been found in a proportion of women of childbearing age in general, some of whom may be struggling to conceive.

Recent scientific discussions recognised the important role of micronutrients in fertility that should be addressed. Micronutrients are essential vitamins and minerals that are required in small quantities as dietary components. Even though these micronutrients do not provide energy to the human body, they are essential for catabolic and anabolic processes and need to be supplied externally.[2] The importance of good nutrition has already been established during pregnancy, influencing embryonic and foetal development, and thus pregnancy outcomes. Overall, supplementation has a small but beneficial effect on fertility in healthy and infertile women, including a shorter time to

This article was accepted: 08 October 2024
Corresponding Author: Gopinath Muruti
Email: gopinathmuruti1982@gmail.com

pregnancy and an increased chance of becoming pregnant.[8] Much less is known about the influence of micronutrient status on female fertility, and human studies are scarce.[12]

This study was conducted to look into the impact of oral multinutrient supplementation on fertility outcome in In vitro fertilisation or Intracytoplasmic sperm injection. The main outcome of this study is to compare the follicular output rate (FORT) between oral multinutrient and folic acid in women undergoing IVF/ICSI.

MATERIALS AND METHODS

This was a prospective pilot study of 50 women, who were planned for IVF/ICSI treatment at the university-based fertility centre in Malaysia from July to December 2023. As a pilot study, power calculation was not required. Women without prior nutritional treatment were consented and assigned to either the multinutrient supplementation as the study group or folic acid daily as control group. Participant information sheets were given to all potential recruits and any inquiries by the participants were answered by the recruiting care provider. The first 25 consecutive women who attended the clinic during the period of study were enrolled into the study group and the subsequent 25 consecutive women into the control group. Women between 19 to 41 years of age were included, whereas those with body mass index more than 35 kg/m^2, women who had taken any multinutrient supplementation preparation other than folic acid alone for the last 3 months and required husband's testicular sperm for treatment were excluded. All recruited women were seen in the clinic as per protocol, routine blood investigations were done and reviewed. At the beginning of the menstrual cycle, transvaginal ultrasound was performed by a sonographer to look for any pelvic pathology, endometrial thickness, bilateral ovaries and total antral follicles count. Investigator gave a phone call to enquire regarding the compliance and any side effects after three weeks of medication initiation. After completion of a minimum of 28 days of the medication, women were advised to call the clinic on her first day of following immediate menstruation to arrange for baseline scan as routine preparation of ovarian hyperstimulation as per local protocol. All patients were given a patient information sheet and signed a written informed consent. The study was approved by the Medical Research Ethics Committee of the University Malaya Medical Centre, Kuala Lumpur, Malaysia (MREC ID No: 2023726-12708, finally approved on December 10, 2023).

Women were treated with a multinutrient preparation (Fortelle + Omega-3, BSV Bioscience Malaysia) consisting of the daily dosage of one soft capsule and one tablet, both taken for at least 28 days prior to ovarian hyperstimulation. The soft capsule contains omega-3 fatty acid (eicosapentaenoic acid (EPA) 119mg and docosahexaenoic acid (DHA) 316mg) and the tablet contains: coenzyme Q10 30mg, vitamin E 45IU, folic acid 800mcg, selenium 76mcg, and catechins 4mg- green tea leaf extract.

While the control group were given one tablet of folic acid 5mg to be taken for at least 28 days prior to treatment. From the literature review, the effects of multinutrient on oocyte recruitment which observed in the follicular phase after antioxidant intake for at least one cycle length. Hence, a minimum of 1 month intake of multinutrient was warranted in our study before a possible effect can be achieved.[2,4]

All women from both groups were using an antagonist protocol for controlled ovarian stimulation, stimulation typically began on day 2 to 4 of menses and ovarian stimulation was started with 200 –300IU of recombinant follicle stimulating hormone (rFSH) alone or Human Menopausal Gonadotropin (HMG) or combination of both. Antagonists (Ganirelix) commenced when the leading follicle reached a diameter of 11 mm. Follicular growth was monitored via a transvaginal ultrasound and FSH dosage was adjusted accordingly. Trigger of ovulation with recombinant human chorionic gonadotropin (Ovidrel) or gonadotropin releasing hormone (GnRH) agonist (Triptorelin) was used for patients who were at risk of ovarian hyperstimulation syndrome (OHSS) when at least 3 follicles of 17 mm in diameter were achieved. Oocyte retrieval was performed 36th hour after trigger. Conventional IVF/ICSI was used for fertilisation.

Data and statistical analysis

The primary outcome was follicular output rate (FORT) which defined as the number of pre-ovulatory follicles (16-20mm) in response to follicle-stimulating hormone (FSH) administration, divided by the pre-existing antral follicle count (AFC) which presented in percentage.[13-14] The secondary outcomes were number of MII oocytes retrieved during oocyte pick-up. MII oocyte is defined as an oocyte at metaphase of meiosis II, exhibiting the first polar body and with the ability to become fertilized.[15-16] Additionally, number of good quality embryos on day 3 after fertilisation. Embryos were divided into those with good quality (embryos with at least 6 cells and a fragmentation rate <20%) and those with poor quality (<6 cell and a fragmentation rate > or equal to 20%)[2] rated by two experienced senior embryologists. Finally, we measured the endometrial thickness before embryo transfer with transvaginal ultrasound and our aim was more than 8mm. As patient and treatment specific parameters, we included age, body mass index, parity, smoking, alcohol consumption, causes of infertility which required IVF such male factor (based on sixth edition of the WHO laboratory manual for the examination and processing of human semen, 2021),[17] polycystic ovarian syndrome -PCOS (by Rotterdam criteria),[18-19] tubal factor infertility, endometriosis and unexplained infertility. The analysis also included duration of infertility in years, the duration of multinutrient or folic acid treatment (in days) until ovarian hyperstimulation, cumulative dose of FSH (in IU) and finally the total days of ovarian hyperstimulation.

Statistical analysis was performed using SPSS version 20. Variables were presented as mean ± standard deviation (SD) for numerical parameters, numbers and frequencies (%) for categorical parameters. For numeric variables, statistical analysis was performed using the Welch test for normally distributed and the Mann–Whitney U test in the case that there was no normal distribution. The chi-square or the Fisher's exact test was used for categorical variables. For all the statistical tests, the level of $p< 0.05$ was taken as significant.

Table I: Basic demographic characteristics of the IVF/ICSI study group and the control group

	Study group (n=25)	Control group (n=25)	p-value
Age, years	36.44 ± 3.33	35.32 ± 3.47	0.250[1]
Body mass index, kg/m^2	25.28 ± 4.12	24.80 ±4.36	0.691[1]
Parity	0.12 ± 0.33	0.48 ± 1.26	0.179[1]
Smoked (%)	0	0	NA
Alcohol consumption (%)	1 ± 4.0	0	>0.999[2]
Male factor (%)	14 (56.0)	11 (44.0)	0.396[3]
Polycystic ovary syndrome (%)	7 (28.0)	4 (16.0)	0.306[3]
Tubal factor (%)	2 (8.0)	7 (28.0)	0.138[4]
Endometriosis (%)	8 (32.0)	6 (24.0)	0.529[3]
Unexplained infertility (%)	3 (12.0)	5 (20.0)	0.702[4]

Data are presented as mean ± standard deviation for numerical parameters or numbers and frequencies (%) for categorical parameters; significance were tested using either.
[1] The Welch test, [2] The Fisher's exact test, [3] Chi-Square test, [4] Fisher's exact test

Table II: Infertility duration, treatment cycle and stimulation progress

	Study group (n=23)	Control group (n=22)	p-value
Duration of infertility in years, mean (±SD)	8.32 ± 3.50	6.08 ± 3.69	0.032[1]
Duration of treatment multinutrient vs Folic acid until ovarian hyperstimulation, days, mean (±SD)	52.96 ± 18.11	57.20 ± 24.89	0.495[1]
IVF treatment cycle, n (%)			
Cycle 1	13 (65.0)	18 (81.8)	
Cycle 2	5 (25.0)	3 (13.6)	0.486[2]
Cycle 3	2 (10.0)	1 (4.5)	
IVF treatment cycle, mean (±SD)	1.45 ± 0.69	1.23 ± 0.53	0.250[1]
Total dose of FSH/LH, mean (±SD)	2410 ± 656.82	2706.82 ± 536.15	0.119[1]
Days of stimulation, mean (±SD)	8.90 ± 2.13	9.68 ± 1.29	0.164[1]

Data are presented as mean ± standard deviation for numerical parameters or numbers and frequencies (%) for categorical parameters; significance were tested using either.
[1] The Welch test, [2] The Fisher's exact test

Table III: Major results of the IVF/ICSI study

	Study group (n=20)	Control group (n=22)	p-value
Follicular output rate, mean (±SD)	68.12 ± 19.47	64.91 ± 20.06	0.493[1]
Number of MII oocytes from mature follicles retrieved, mean (±SD)	6.65 ± 3.84	6.09 ± 3.01	0.626[1]
Number of good quality embryo on day 3 after fertilisation, mean (±SD)	4.00 ± 3.10	3.45 ± 2.30	0.549[1]
Endometrial thickness before embryo transfer, mean (±SD)	10.35 ± 1.32	10.36 ± 2.04	0.320[1]

Data are presented as mean ± standard deviation; significance were tested using either.
[1] The Welch test

RESULTS

Patient characteristics parameters were similar between the study and the control groups (Table I). All the patients in both groups underwent antagonist protocol. There was total 8 patients (study group n=5; control group n=3) were excluded from primary and secondary outcomes analysis (2 patients in study group had spontaneous pregnancy prior starting IVF and 3 patients converted to IUI during the course of stimulation, in control group 1 had spontaneous pregnancy and 2 patients refused IVF after completed treatment). According to patients' statements all women had correctly adhered to the supplementation regimens.

There is no difference in the mean age of women in both groups (36.44 ± 3.33years; 35.32 ± 3.47 years). The mean body mass index was comparable between the two groups. The duration of multinutrient and folic acid treatment in both groups, treatment cycle and stimulation progress were similar (Table II). There was no difference in the FORT after multinutrient supplementation as compared to the folic acid group. However, in this study we observed that the mean FORT in the multinutrient group was slightly higher compared to the control group (68.12 ± 19.47 vs 64.91 ± 20.06, p=0.493) (Table III). The mean number of MII oocytes retrieved from mature follicles and number of good quality embryo on day 3 after fertilisation were not statistically significant between the two groups (6.65 ±3.84 vs 6.09 ± 3.01, p=0.626 and 4.00 ± 3.10 vs 3.45 ± 2.30, p=0.549, respectively). In addition, there were no differences in endometrial thickness before embryo transfer in both groups (10.35 ± 1.32mm vs 10.36 ± 2.04mm, p=0.320). However, we perceived that the total dose of FSH and duration of

controlled ovarian stimulation were lower in the study group compared to control group (2410 ± 656.82 IU vs 2706.82 ± 536.15 IU, p= 0.119 and 8.90 ± 2.13 days vs 9.68 ± 1.29 days, p=0.164, respectively) (Table II).

DISCUSSION

This prospective controlled trial demonstrated that the use of multinutrient supplementation containing Omega 3, coenzyme Q10, folic acid, selenium, vitamin E and catechins led to higher follicular output rate compared to folic acid although did not reach statistical significance. Commonly, in assisted reproductive techniques, follicular recruitment and development in response to controlled ovarian hyperstimulation (COH) with gonadotropins are key elements and essential in the treatment of infertility.[20] In addition, ovarian responsiveness is one of the most commonly studied parameters in clinical research concerning IVF treatment, in which in our study we observed the FORT. Hypo-responsiveness to follicle stimulating hormone in controlled ovarian stimulation is a phenomenon manifests as a low follicles output rate (FORT) with a discrepancy between the relatively low number of pre-ovulatory follicles which develop following ovarian stimulation as compared to the number of antral follicles available at the start of stimulation. Normal responder is a phenomenon where the age of the women or ovarian reserve or previous ovarian response, predicted to result in a not too low, or too high ovarian response. The definition of normal responders is based on predicted response only; some women might have had an unexpected, exaggerated response while some others an unpredicted poor response. This limitation has been accepted, in absence of any better marker to denote 'normal responder'. On the other hand, hyper-responder is a condition where women were predicted to yield high ovarian response based on high AMH and/or high AFC and/or exaggerated follicular response in the previous cycle, except where a diagnosis of typical polycystic ovary syndrome (PCOS) was made. Multinutrient supplementation in women with fertility problems can help normalise trace element levels, which may have a positive impact on the quality of the microfollicular environment, and thus on oocyte and embryo quality, implantation, and live birth.[5,21] Camilia Bessow et al, mentioned that the number of oocytes retrieved is the main outcome measure of ovarian responsiveness to gonadotropin stimulation.[22] However, the number of pre-ovulatory follicles obtained at the end of COH is not a reliable reflection of the antral follicle sensitivity to FSH, and it is strongly correlated with the number of antral follicles before ovarian stimulation. Although maybe not only the number of antral follicles, but also their size, is important.[23] Therefore, we assessed the FORT and it is known to be correlated to the outcomes of IVF, including pregnancy rates. In our centre, not all patients had AMH before ovarian stimulation as it is indicated only for older women or for those who had prior ovarian surgery, as AMH can be one of the predictors of ovarian response to FSH. In contrast, AFC is routinely measured at the beginning of the cycle as there will be a cycle-to-cycle variation. However, we consider this as one of our study limitations and more future research is warranted on this matter.

As mentioned earlier, the mean number of MII oocytes retrieved from mature follicles in this study was not statistically significant between the two groups. Previous studies had shown that women with a diet high in EPA and DHA have the fewer MII oocytes.[24] Similarly, Hammiche et al. demonstrated that high intakes of EPA and DHA reduced oestrogen response and the number of follicles after ovarian stimulation.[25] Correspondingly, a study on rats fed a diet high in EPA and DHA showed a decline in frequency of ovulation.[26-27] The reduction in PGF2α involved in follicle growth and ovulation which was attributed to EPA and DHA may relatively explain the reduced number of MII oocytes.[28-29] Despite the inverse relationship between EPA intake and the number of MII oocytes from previous studies, it has been revealed that consuming monounsaturated fatty acids (MUFA) such as EPA could increase the fertilisation rate. Indeed, it was demonstrated that the gene expression of insulin-like growth factor-I (IGF-I) in granulosa cells increased by EPA could improve the fertilisation rate and embryo development.[30] More future research is needed to evaluate the impact of EPA and DHA on fertility outcome. We could not draw any conclusion from our study in regards to the use of Omega 3 fatty acid especially EPA and DHA as our sample size was small and we believe it's our study limitations.

Moreover, the use of multinutrient supplementation Fortelle + Omega -3 in this study revealed a slightly higher number of good quality embryos on day 3 after conventional IVF or ICSI treatment compared to the use of 5mg folic acid alone although not clinically significant. Kazem et al. in a prospective study demonstrated that multinutrient ingestion can significantly improve embryo quality in older women (>35 years) undergoing IVF/ICSI.[2] In addition, the use of the multinutrient resulted in a significantly higher fertilisation rate compared with folic acid only (66.7% vs 42.9% respectively) and a higher proportion of women with at least 1 good-quality embryo (58% vs 36%, respectively), supporting a beneficial effect of multinutrient supplementation on female fertility that may be due to the effects of the antioxidants within the formulation.[2]

Furthermore, we concluded that there is no significance achieved on endometrial thickness before embryo transfer between both groups. However, in a prospective randomised controlled trial by Cicek et al. demonstrated that in women with unexplained infertility undergoing controlled ovarian stimulation, supplementation with multinutrient especially vitamin E significantly increased endometrial thickness compared with no supplementation.[31] Supplementation was thought to improve the endometrial response via the antioxidant effects of vitamin E which has been shown to reduce oxidative stress and its anticoagulant effects by increasing endometrial and follicular blood supply.[31] A recent study by Marcus et al. revealed that the mean serum AMH levels and endometrial thickness values were significantly higher after 3 months micronutrient supplementation as compared to baseline.[4]

Coenzyme Q10 (CoQ10) is a lipid-soluble quinone, acting as an effective antioxidant, which prevents lipid peroxidation and DNA oxidation.[32] El Refaeey et al. in his study has

mentioned that oral CoQ10 supplementation in PCOS women increased the mean number of mature follicles (> 18 mm) and the ovulation rate per cycle (65.9% vs. 15.5%, p < 0.001) compared with no-treatment.[33] In another study in poor ovarian response women, CoQ10 increased the median number of oocytes retrieved and fertilised and increased the median number of day 3 high-quality embryos when compared with no-treatment.[34-35]

Selenium (Se) is an important micronutrient for several vital functions, such as deoxyribonucleic acid (DNA) synthesis, modulation of the thyroid metabolism and an antioxidant.[36] Luiz G et al. in his systematic review revealed that selenium supplementation increases number of oocytes and follicles after stimulation in IVF, increases concentration of antioxidants in follicular fluid, maintains serum selenium level during pregnancy and decreases antithyroid antibody levels in women with autoimmune thyroid disease.[37]

Vitamin E's antioxidant properties may protect both the mother and baby throughout pregnancy by acting as a chain-breaking antioxidant and the body's primary lipid peroxyl radical scavenger, hence reducing the likelihood of complications during pregnancy.[38] Cicek et al. suggested that vitamin E, through its antioxidant action, may enhance the endometrial environment and thickness in women with unexplained or idiopathic infertility.[31] Bahadori et al. had mentioned that optimal concentration of Vitamin E in follicular fluid essential for the highest percentage of metaphase II oocytes and higher quality embryos.[39]

Green tea catechins have been reported to exert antioxidative effects in humans.[2] In animal study with endometriosis, it enhances anti proliferative properties by reducing development of endometriosis lesions and anti-angiogenic properties by reducing angiogenesis of endometriotic lesions. On the other hand, in a clinical trial patient with polycystic ovarian syndrome (PCOS) green tea catechins decreases rises of testosterone and reduces fasting insulin on overweight and obese PCOS women.[40]

It is well established that folic acid supplementation is vital to reduce the risk of neural tube defects. Patients in the control group were given Folic Acid 5mg for at least 1 month prior to ovarian stimulation. We choose to use Folic acid 5mg as it is the only preparation widely available in our hospital as well as the Ministry of Health Malaysia.

Finally, Omega 3 fatty acids introduced through a multivitamin or single compound supplementation may be beneficial in terms of fertilisation rates and embryo quality as well as a high intake of oils rich in omega-3 was observed to improve oestradiol levels, ovulation, follicles development and embryo morphology.[2,26]

In this pilot study, we focused on follicular output rate as the major outcome parameter. Although multinutrient widely researched in female fertility outcome, no studies reported on the FORT, an important marker for IVF outcomes. This study was aimed at evaluating the FORT between the both study groups. In this study we observed that the mean FORT in the multinutrient group was slightly higher compared to the control group although no statistical significance. Future studies are therefore warranted to confirm the clinical effect of the tested multinutrient supplementation mainly in FORT.

Our results must be interpreted with care due to the design as a pilot study, although controlled no proper randomization done with a small sample size without a prior sample size calculation which we consider to be the limitations of the study. Recruited women in both groups might have different dietary profiles with various nutritional status, which such bias would likely lead to a reduction of the beneficial effects observed in the study group. Ideally, to test the serum levels of the supplemented multinutrient before and after treatment which was not done in our trial. Notably, we assume that some women of the control group who had informed about the beneficial effect of multinutrient might have bought the preparation or another multinutrient similar to that on their own. Such a bias would likely lead to a reduction of the beneficial effects observed in the study group. Last but not least, the embryologist's intraobserver variability in the scoring was not evaluated, which might have introduced some bias as well. This study provides preliminary evidence that multinutrient supplementation increases follicular output rate, higher number of MII oocytes and good quality embryos on day 3 after fertilisation though no clinical significance. We perceived that the total dose of follicle stimulating hormone and duration of controlled ovarian stimulation were lower in the study group. There is a need for a multicenter, randomised controlled trial with larger sample size to validate the positive effects of multinutrient in female fertility.

CONCLUSION

In conclusion, a multinutrient supplementation such as Omega 3, coenzyme Q10, folic acid, selenium, vitamin E and catechins given for a minimum of 28 days, may have a positive effect on FORT. More research is warranted to prove this effect.

ACKNOWLEDGMENT

The authors would like to thank BSV Bioscience Malaysia for providing Fortelle + Omega 3. All the authors have made substantial contributions in relation to the research design, the statistical analysis and interpretation and approved the final version of this document.

DISCLOSURE STATEMENT

The authors report no conflicts of interest.

REFERENCES

1. Malaysia Fertility Rate 1950-2023. Available from: https://www.macrotrends.net/countries/MYS/malaysia/fertility-rate [cited July 2023]
2. Kazem N, Katharina W, Andrea W, Martin I, Christian E, Johannes O, et al. The Impact of a Standardized Oral Multinutrient Supplementation on Embryo Quality in In vitro Fertilization/Intracytoplasmic Sperm Injection: A Prospective Randomized Trial. Gynecol Obstet Invest 2017; 82: 8-14

3. Markus L, Judith A, Hannah I, Clara H, Michaela S, Patricia W et al. The effect of micronutrient supplementation on serum anti-Mullerian hormone levels: A retrospective pilot study: Gynecol Endocrinol 2022; 38(4): 310-13
4. Marlene H, Kazem N, Martin I, Christian E, Johannes O. The Impact of a Standardized Micronutrient Supplementation on PCOS-typical parameters: A Randomized Controlled Trial. Arch Gynecol Obstet 2019; 300(2): 455-60
5. Kelsey T, Anderson R, Wright P, Nelson S, Wallace W. Data-driven assessment of the human ovarian reserve. Mol Hum Repro 2012; 18(2): 79-87
6. Gynnerup A, Lindhard A, Sorensen S. The role of anti-Mullerian hormone in female fertility and infertility - An overview. Acta Obstet Gynecol Scand 2012; 91(11): 1252-60
7. Showell M, Brown J, Clarke J, Hart R. Antioxidants for female subfertility. Cochrane Database Syst Rev 2013, 8:CD007807.
8. Ella S, Deborah N. The Impact of Preconceptional Multiple - Micronutrient Supplementation on Female Fertility. Clinical Medicine Insights: Women's Health 2019, (12): 1–6
9. Agarwal A, Gupta S, Sikka S. The role of free radicals and antioxidants in reproduction. Curr Opin Obstet Gynecol 2006; 18: 325-32.
10. Twight J, Bolhuis M, Steegers E, Hammiche F, Inzen W, Laven J et al. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum Reprod 2012; 27: 2526-31
11. Grajecki D, Zyriax BC, Buhling KJ. The effect of micronutrient supplements on female fertility: A systematic review. Arch Gynecol Obstet 2012; 285:1463-71
12. Urman B, Oktem O. Food and drug supplements to improve fertility outcomes. Semin Repro Med. 2014; 32(4): 245-52
13. Georg G, Valerie T, Christine M, Jane R. Comparison of the follicular output rate after controlled ovarian stimulation with daily recombinant follicle-stimulating hormone versus corifollitrophin alfa. Eur J Obstet Gynaecol Reprod Biol 2019; 232: 101-05
14. Fernando Z, David A, Silke D, Catherine R, Jacques D, Rebecca S et al. The International Glossary on Infertility and Fertility Care. Fertility and Sterility 2017; 108 (3): 393-406
15. Bei S, John Y. Identifying fertilization-ready metaphase II stage oocytes beyond the microscope: A proposed molecular path forward. Fertil Steril Rev 2021; 2(4): 2666-5719
16. Misty B, Steven G. Pelvic Imaging in Reproductive Endocrinology. Yen & Jaffe's Reproductive Endocrinology, Physiology, Pathophysiology and Clinical Management, Eight Edition, 2019
17. World Health Organization, Geneva 2021. WHO laboratory manual for the examination and processing of human semen, sixth edition. Licence: CC BY-NC-SA 3.0 IGO [cited July 2023] Accessed from https://iris.who.int/bitstream/handle/10665/343208/9789240030787-eng.pdf?sequence=1
18. Razieh M, Mina R, Mahin T. Evaluation of oocyte quality in Polycystic ovary syndrome patients undergoing ART cycles. Ferti Res and Pract 2021; 7(1): 2.
19. Banafshe H, Ghazaleh E. Association of Micronutrient Intakes with Female Infertility: Review of Recent Evidence. Thrita J Neu 2015; 4(1): e25586
20. Li HWR, Lee VCY, Ho PC, Ng EHY. Ovarian sensitivity index is a better measure of ovarian responsiveness to gonadotrophin stimulation than the number of oocytes during in-vitro fertilization treatment. J Assist Reprod Gene. 2014; 31:199–203.
21. Lai Q, Chen C, Zhang Z, Zhang S, Yu Q, Yang P et al. The significance of antral follicle size prior to stimulation in predicting ovarian response in a multiple dose GnRH antagonist protocol. Int J Clin Exp Pathol 2013; 6: 258–66.
22. Camilia B, Rafaela D, Tatiane DS, Rita C, Vanessa G, Joao S. Antral follicle responsiveness assessed by follicular output rate (FORT) correlates with follicles diameter. J Ovarian Res 2019; 12(1): 48.
23. Tomás C, Nuojua-Huttunen S, Martikainen H. Pretreatment transvaginal ultrasound examination predicts ovarian responsiveness to gonadotrophins in in-vitro fertilization. Hum Reprod 1997; 12: 220–3.
24. Maryam J, Mahboube T, Mohammad H, Motahar H, Gholam H. Dietary Fatty Acid Intakes and the Outcomes of Assisted Reproductive Technique in Infertile Women, J Reprod Infertil 2021; 22(3): 173-183
25. Hammiche F, Vujkovic M, Wijburg W, de Vries JH, Macklon NS, Laven JS, et al. Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. Fertil Steril 2011; 95(5): 1820-3.
26. Broughton KS, Rule DC, Ye Y, Zhang X, Driscoll M, Culver B. Dietary omega-3 fatty acids differentially influence ova release and ovarian cyclooxygenase-1 and cyclooxygenase-2 expression in rats. Nutr Res 2009; 29(3): 197-205.
27. Mattos R, Staples CR, Williams J, Amorocho A, McGuire MA, Thatcher WW. Uterine, ovarian, and production responses of lactating dairy cows to increasing dietary concentrations of menhaden fish meal. J Dairy Sci 2002; 85(4): 755-64.
28. Amaya-Montoya C, Matsui M, Kawashima C, Hayashi KG, Matsuda G, Kaneko E, et al. Induction of ovulation with GnRH and PGF (2 alpha) at two different stages during the early postpartum period in dairy cows: ovarian response and changes in hormone concentrations. J Reprod Dev 2007; 53(4): 867-75
29. Shahnazi V, Zaree M, Nouri M, Mehrzad-Sadaghiani M, Fayezi S, Darabi M, et al. Influence of ω-3 fatty acid eicosapentaenoic acid on IGF-1 and COX-2 gene expression in granulosa cells of PCOS women. Iran J Reprod Med 2015; 13(2): 71-8
30. Toori MA, Mosavi E, Nikseresht M, Barmak MJ, Mahmoudi R. Influence of insulin-like growth factor-i on maturation and fertilization rate of immature oocyte and embryo development in NMRI mouse with TCM199 and α-MEM medium. J Clin Diagn Res 2014; 8(12): AC05-8.
31. Cicek N, Eryilmaz OG, Sarikaya E, Gulerman C, Genc Y. Vitamin E effect on controlled ovarian stimulation of unexplained infertile women. J Assist Reprod Genet 2012; 29: 325–28.
32. Rodick T, Seibels D, Jeganathan R, Huggins K, Ren G, Mathews S. Potential role of coenzyme Q10 in health and disease conditions. Nutr Diet Suppl 2018; 10: 1–11.
33. El Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate resistant polycystic ovary syndrome. Reprod BioMed Online 2014 29(1): 119–24.
34. Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: A randomized controlled trial. Reprod Biol Endocrinol 2018; 16(1): 29.
35. Sen SD. Co-enzyme q10-a mitochondrial antioxidant -a new hope for success in infertility in clomiphene-citrate-resistant polycystic ovary syndrome. BJOG 2017; 124: 9.
36. Qazi IH, Angel C, Yang H, Pan B, Zoidis E, Zeng CJ, et al. Selenium, selenoproteins, and female reproduction: A review. Molecules 2018; 23(12): 3053
37. Luiz G, Andre M, Tiago D, Ricardo Z, Camila M, Andrielle C, et al. Relation between Selenium and Female Fertility: A Systematic Review, Rev Bras Ginecol Obstet 2022; 44(7): 701–9.
38. Anderson Berry, AL, Hanson, CK. The role of vitamin E in pregnancy. In Vitamin E in Human Health; Springer: Berlin/Heidelberg, Germany, 2019: 405–17.
39. Bahadori, MH, Sharami, SH, Fakor, F, Milani, F, Pourmarzi, D, Dalil-Heirati, SF. Level of Vitamin E in Follicular Fluid and Serum and Oocyte Morphology and Embryo Quality in Patients Undergoing IVF Treatment. J. Fam. Reprod. Health 2017; 11(2): 74–81.
40. Datu A, Norizam S, Siti Sarah M, Mohd Helmy M. Beneficial Effects of Green Tea Catechins on Female Reproductive Disorders: A Review, Molecules 2021; 26(9): 2675.

Parental perception on home therapy and its associated factors for children with cerebral palsy: A qualitative study in Malaysia

Thanalactchumy Chandrabose, MMed (Rehab Med) (UM)[1], Subapriya Suppiah, MMed (Rad) (UM), FANMB[2], Aishah Ahmad Fauzi, MMed (Rehab Med) (UM)[3], Julia Patrick Engkasan, PhD(Mal)[4], Muhammad Hibatullah Romli, PhD(Sydney)[1]

[1]Department of Rehabilitation Medicine, Universiti Putra Malaysia, [2]Pusat Pengimejan Diagnostik Nuklear, Universiti Putra Malaysia, [3]Department of Rehabilitation Medicine, Daehan Rehabilitation Hospital Putrajaya, [4]Department of Rehabilitation Medicine, University Malaya, Malaysia

ABSTRACT

Introduction: Children with cerebral palsy (CP) benefit from consistent rehabilitation intervention. Home therapy (HT) consists of therapeutic exercises and activities targeting physical and functional improvement. HT is vital to ensure the rehabilitation provided in the clinical setting is further continued by the client. However, the success of HT mostly depends on compliance and support from caregivers, especially the parents. The objective of this study was to explore parents' perceptions of home therapy and to identify facilitating factors and barriers to it.

Materials and Methods: An interview-based qualitative study was conducted in a public university hospital in Malaysia, utilizing in-depth interviews. Audio recordings of the interviews were transcribed verbatim. The transcript data were coded, and the codes were then organized into themes using a thematic analysis approach.

Results: Data from twelve mothers and three fathers among a total of fifteen children with CP were acquired. Nine themes were derived from transcript data namely : HT is a simple home prescription,HT empowers and enhances experiences of care, Negative experience, goal-directed positive attitude, External Support System, physical health as a barrier, psychological health as barrier, limited time and limited external support system.

Conclusion: Real-life experiences of parents with CP children regarding HT was explored and valuable outcomes were derived from this study to help clinicians to manage children with CP more efficiently and understand their family dynamics better in the local context. Overall, parents perceived HT as doable and it provided physical, functional, and psychological benefits for them as well as improved their confidence and skills to perform exercises on their children and empowered them to monitor their children's progression.

KEYWORDS:
Perception of Home Therapy, Cerebral Palsy, Qualitative Study

INTRODUCTION

Cerebral palsy (CP) is a group of disorders of movement and posture, causing activity limitation that is attributed to non-progressive disturbances occurring in the developing fetal or infant brain.[1] The prevalence of CP in developed countries is 1.5-2.0 per 1000 live births.[2-5] In Malaysia, the data on the prevalence of CP is limited, however, it is estimated to be slightly higher. In 2012, the Ministry of Health registered 215 cerebral palsy children under disability registry .CP is a chronic childhood condition comprised of various motor and non-motor symptoms.[6-8]

Most interventions for cerebral palsy involve comprehensive approaches which are medical optimization, spasticity management, physiotherapy, occupational therapy, speech therapy, orthotics, aids and equipment prescription, and corrective surgery.[9] Besides these approaches, HT ensures the continuity of the rehabilitation program where the clients (i.e., caregivers/parents) were prescribed and educated on the rehabilitation training by the therapists for the caregiver to conduct at home–which is tailored to be feasible and doable using the existing resources at home.[10] HT is a useful strategy for increasing the frequency of therapy when added to regular hospital-based exercises.[11] Goal-directed HT has evidence to provide an increased dose of therapy to improve hand function and ambulation.[10-12]

There are very limited data published on HT for children with CP in Malaysia. It is still unknown to many practitioners or healthcare workers who actively manage CP patients, regarding the prescription of HT and its associated factors in Malaysia. Sadly, during most of the clinic settings, noted parents were found to be not compliant with HT. Novak, in his paper on parents' experience in implementing HT, found that parents generally perceived positive experiences and expressed that HT has multiple benefits for both parents and children.[13] Parents in this study perceive HT as a form of guidance and advice that can be practiced at home to maximize their children's potential as well as increase their confidence to help their children. Hinojosa J, explored the perception of mothers about HT and found that mothers are the main carer, and most of them were stressed about the care for their children including performing HT.[14]

This article was accepted: 08 October 2024
Corresponding Author: Thanalactchumy Chandrabose
Email: thanalactchumy@upm.edu.my

In a recent study by Demeke ZD, parents perceived HT as important to increase the frequency of training.[15] However, the same study found that there are barriers to implementing HT such as lack of awareness of the importance, lack of support from other family members, and mothers who are the main carers were drained out with other chores and unable to perform HT. Common factors that influence compliance to exercise in hospital settings are parental readiness, the time factor, cooperation and motivation of children, characteristics of the exercise, therapist communication and guidance, and availability of equipment.[16] Although this information has been already studied and published, however, there is a limited understanding of such factors that were also experienced by Malaysian parents with cerebral palsy children in practicing HT.

Hence the primary objective of this research is to explore parents' perception including their understanding and experience with HT, while secondary objectives will be identifying facilitating and limiting factors in performing it. This investigation is important to determine whether we can translate some existing evidence to our local context use, or whether some unique aspects are identified that require for original solution.

MATERIALS AND METHODS

This is a qualitative study utilizing an in-depth interview (IDI) that was conducted based on the guideline by Ryan and colleagues and conceptualized by a hermeneutic phenomenological approach.[18] It is important to collect information that can be produced more consciously from a person's own experience which is fundamental in human-related studies. A qualitative study is a powerful method to explore a richer information gathering and deeper understanding beyond what is presumed by the researcher.[19] Qualitative study also provides insight generation to the participants which creates more information development.[20] In this study, we have adopted the concept of the International Classification of Functioning, Disability, and, Health -Children and Youth version (ICF-CY) model as the study framework. ICF has six domains which are health, body impairment, activity limitation, and restriction in participation which are influenced by contextual factors namely personal and environmental. It is specific to children and commonly used in clinical and research involving CP. In this study, the objectives are based on ICF-CY enabling the covering of all important 6 domains for comprehensive results.[21]

Participantsand recruitment

Participants for this study were recruited via purposive sampling method considering characteristics varieties. Inclusion criteria were the mother or father (being the main carer) of children with a primary diagnosis of cerebral palsy with severity of Gross Motor Functional Classification System (GMFCS) of I-V, aged 3 to 17 years old, undergoing outpatient therapy at Paediatric Rehabilitation Clinic follow-up in University Malaya Medical Centre (UMMC) and the parents must be able to communicate in either English/Malay.

Participants were recruited from those attending therapy at the department. Both primary investigator and co-investigator (AAF) screen potential participants. Agreed participants were arranged for a meeting according to their convenience. Before the agreement, each prospective participant was explained about the study and provided with a consent form. The prospective participants can refuse to participate while their rights are ensured. This study received ethical approval from the University of Malaya Medical Centre – Medical Research Ethics Committee (MREC ID NO: 2018226-6053). The recruitment duration was from 11th June 2018 until 15th January 2019.

Procedure and data collection

All the interview was conducted by primary investigator to avoid any conflict of interest as no previous relationship between the primary investigator and participant. All the interviews were conducted in a dedicated room at the university hospital except one which was conducted at the participant's home. Anonymity and confidentiality were ensured when the room was informed in use during the session and no one was allowed to enter during the session. The session was guided by a set of semi-structured questions but not followed prescriptively. The semi-structured questions were developed based on the objectives of this study, where it became a framework to steer the discussed topic and allow flexibility in which the questions evolved throughout the interview to explore more information until data saturation (Table I). The session begins with establishing rapport and collecting demographic information followed by generic to specific or personal questions. The researcher's role is as an active listener to create a mutual and non-intimidating atmosphere and as a facilitator without providing any comments or instilling judgment. The interviews ranged from 15 to 45 minutes (average thirty minutes) each. The interview was audio recorded with two recorders. Each interview session is followed by a reflection session by the primary investigator and co-investigator to review the responses, interview questions, and interview techniques.

Data analysis

Each recorded conversation was transcribed verbatim by the researcher(TCB). Participants were given pseudonyms in the transcript to maintain anonymity.[22] Participants were provided with the transcripts for a member-checking procedure to maintain the accuracy of data.[23] Thereafter, the data were analyzed using the thematic analysis technique. Thematic analysis (TA) is a tool to form a framework by finding a pattern in the research that answers the objective of the study.[24] First part of the thematic analysis is to find codes which are smaller units of building blocks that can be categorised together to form themes.[24] In this study TA conducted based on the reference by Naeem et al.[25] The transcripts were read and re-read by two researchers (TCB, AAF) independently. Coding started by identifying sentences that meet the objective and labeled with descriptive words which were then listed down manually in soft copies. The investigators met several times to compare the codes and revised them to ensure the codes matched the objectives, and then together mapped all codes again manually on paper. Codes with similar meanings were grouped into the same category. Subsequently, the data were read again a few times independently and several categories were formed from all

available codes. Finally, themes were formed from similar categories to answer the study objectives. Themes and their categories were mapped manually on a paper by each researcher and compared among until reach more than 90 percent of inter-rater agreement.[25] Final themes were agreed upon and confirmed with the third investigator(JAP), who has experience in qualitative study analysis but was not involved in the data collection and who did know the research participants.

RESULTS

A total of 15 participants agreed to interview among 18 that were selected. This sample size is based on data saturation, in which no further new information was obtained from parents.[25] Among these parents, three were fathers, and one of them quit his job for full-time care. Otherwise, caregivers were mothers, of whom six were housewives and six were still working. Four of the working mothers were professionals, working as a teacher, accountant, nurse, and doctors. The CP children in this study varied from GMFCS level I to V. There were a total of eight children with severe GMFCS 21 levels of IV to V, and among them, four children were enrolled in a special government school. On the other hand, seven children were GMFCS level I to III, and all were attending school. Table II shows the description of participants and children. After TA, nine themes were derived from the data.

SECTION 1: Perception of parents

Theme 1: HT is a simple home prescription

HT is a continuation of the rehabilitation learned

Parents perceive HT as an assignment to be completed at home after their therapy session in the hospital. HT provides the frequency to maintain the treatment effect. It can be done at any time convenient to parents. It is prescribed according to the targeted aim.

"…my understanding of this home exercise program is a series of exercises to be carried out at home so that we can do it for our children every day or at our extra time because the time that we spend in the hospital probably once a week or twice a week …all these exercises has been prescribed by the physiotherapist after they have assessed his condition." (mother 3)

"For me, I understand that this is in addition from doing it in the hospital. When he's in the hospital, he doesn't have a lot of slots, sometimes full. So, at least we make it at home daily, so can improve his muscle tone. Not depending on the hospital only. So, I have that understanding." (mother 8)

Nature of prescribed therapy

Parents further describe HT as a set of feasible exercises and meaningful activities that require no special equipment. It can be performed with items or toys that are available at home.

"Sometimes I would exercise him, I would throw a ball near him and he will try to catch it, and he would throw again." (father 2)

"Ha stretching her hand and leg. Then the hand she always keeps in fits, I'll open, ha stretching. Then I would sit her in the car seat for an hour, and then we hold her. My husband holds her feet, I hold her body, and we raise her." (mother 12)

Theme 2: HT empowers and enhances experiences of care

Optimize the care level

In this study, parents reported that by practicing regular HT, their skill in monitoring the progress and performance of the children improved.

"We are the mother doing for the child; so, we also can know his/her progress. We can keep monitoring." (mother 3)

They felt empowered and could understand their child's condition better even when their children could not express themselves clearly.

"I know he has a way, so I can help him, I know. When you are close to him, you will know it." (mother 8)

"I knew how to care for him and able to know when he wants something." (mother 5)

Parents also become confident in helping their children to perform exercises to improve their impairment and achieve targeted goals.

"I'm confident. I have more confidence in me which lead me to take more effort to improve my son." (father 2)

Optimization of resources

The above results refer to saving time and cost for traveling. It also refers to saving money spent on the severity of the disease as the impairment improves after persistent HT. In this study, two mothers who regularly perform HT, and whose child has a severe type of CP, reported that HT reduces the time spent traveling to the hospital. It also saves the costs incurred for their journey.

"That's why when I go for an appointment, let's say that appointment is for one hour; but it can be only up to thirty minutes because my son becomes tired and moody easily due to the long journey. So, it was like a waste of my time and expenses. So, I feel like I have to do it at home." (mother 8)

Caring for a CP child involves costs related to their care and equipment. The more severe the disability, the more expenses were expected. However, with HT, when the impairment was managed well, it led to an improvement in function. This has reduced the cost of certain items in their care.

"These couple of years her sports shoes last for one year which is longer compared to previous years. So, I know that she is improving and not worsening. At least the one I'm very concerned about is her sports shoes. How long do I have to buy a new one." (mother 1)

Optimization of physical and psychological function

Parents describe that after practicing HT, they could notice improved body structure, activity, participation, and independence. Parents in this study know that HT should be done consistently for a positive outcome.

"Now he can walk longer duration. He can follow me for shopping. Not using his wheelchair, also can stand long." (mother 5)

Table I: Demographic characteristics of the participants

No.	Name of child	CP Type	Child age (in years)	GMFCS level	Child gender	Parent Interviewed	Schooling Status	Venue
1	GSS	Right Hemiplegic	14	I	Female	Mother 1	Yes	Hospital Lobby
2	IM	Triplegic	9	II	Male	Mother 2	Yes	Hospital Gym
3	WK	Diplegic	9	III	Male	Mother 3	Yes	Patient's Home
4	TD	Diplegic	4	II	Male	Mother 4	Yes	Rehabilitation Clinic
5	XY	Diplegic	15	III	Male	Mother 5	Yes	Hospital Gym
6	SF	Diplegic	8	II	Female	Father 1	Yes	Hospital Gym
7	LH	Diplegic	6	II	Male	Father 2	Yes	Hospital gym
8	FR	Diplegic	7	IV	Male	Father 3	Yes	Hospital gym
9	AM	Diplegic	7	IV	Male	Mother 6	Yes	Hospital gym
10	NA	Quadriplegic	3	V	Female	Mother 7	No	Postnatal Ward
11	MH	Quadriplegic	5	IV	Male	Mother 8	No	Rehabilitation Ward
12	HD	Quadriplegic	5	V	Male	Mother 9	Yes	Rehabilitation Clinic
13	WZB	Quadriplegic	7	IV	Male	Mother 10	Yes	Rehabilitation Ward
14	NQ	Quadriplegic	7	IV	Female	Mother 11	No	Rehabilitation Clinic
15	WNA	Quadriplegic	4	IV	Female	Mother 12	No	Hospital Gym

Table II: Semi-Structured Interview Questions For In-Depth-Interview

NO	SEMI-STRUCTURED INTERVIEW QUESTION FOR IDI
1	What is your understanding of a HEP that is prescribed by a physiotherapist and occupational therapist to your child?
2	Can you tell me if there are any changes to your child after performing HEP?
3	Can you describe what are the benefits/impacts of a HEP on you, your child, and your family?
4	What is the barrier for you to engage your child to do or perform a HEP?
5	What are the motivating factors for you to engage your child to do or perform a HEP?
6	What is the barrier for your child to do or perform a HEP?
7	What are the motivating factors for your child to do or participate in a HEP?
8	Do you have any suggestions on how to improve the HEP?

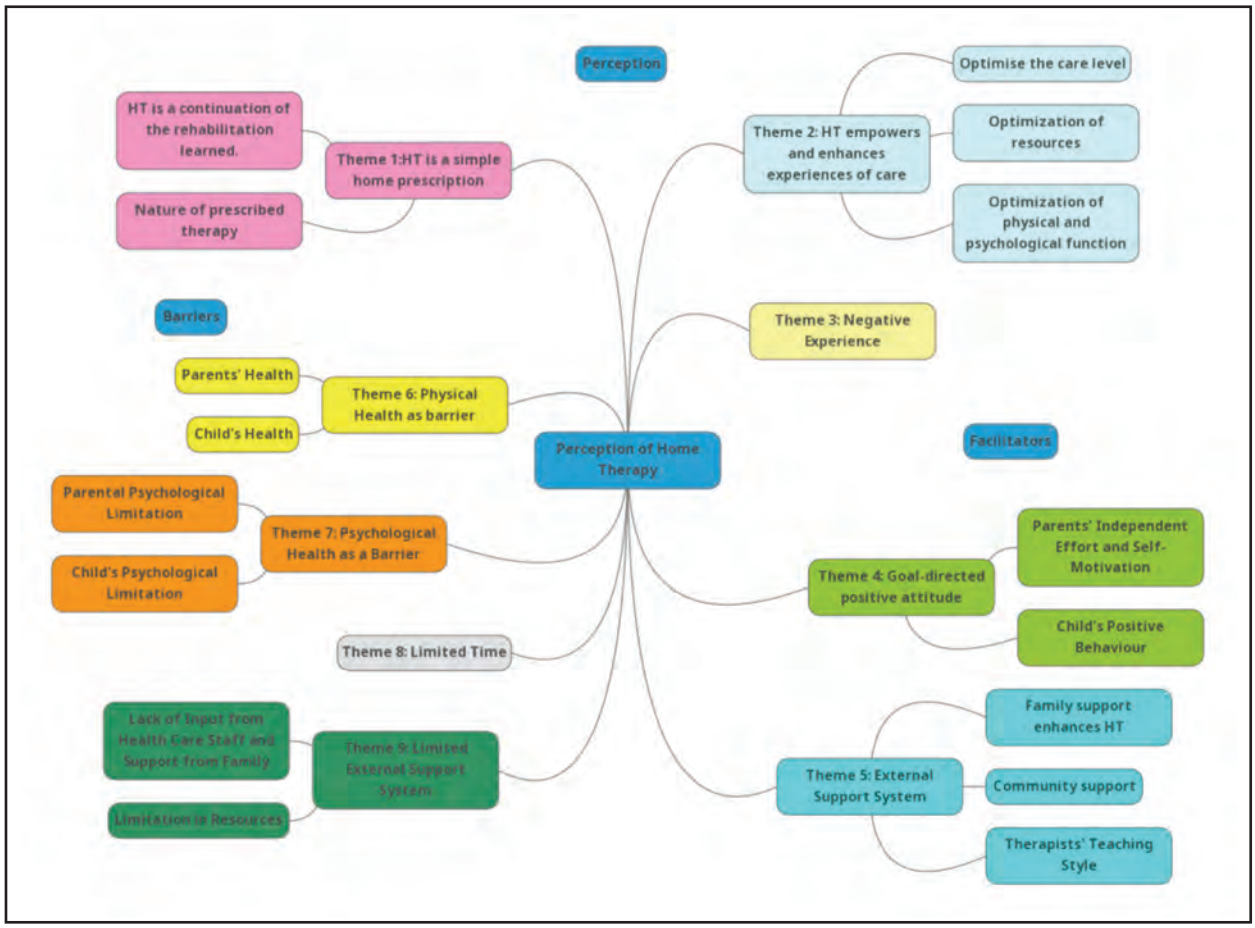

Fig. 1: Thematic Diagram for Factors Associated with Perception of Home Therapy

"I think it will most likely be subtler. I mean, because we are doing it quite regularly, so we don't really realize any like regression. So, not noticing if there is a bit stiffer if we don't do it. Because we kind of do it regularly." (mother 4)

Most parents noted positive psychological changes in their children in which they gained confidence in mobility and participation in functional activity.

"he is brave now, he has confidence in himself, he watches for himself while walking with reverse walker. He even could hold the spoons even though not feeding himself." (father 2)

Theme 3: Negative Experience
Among the fifteen parents, two parents found to have negative experiences during HT. They were namely, non-sustainable positive effects and fear of fall.

I stopped it (home therapy) and the progression stopped. But when I do that there is a change in it though not much." (mother 2)

"I am worried to help my child to walk at home, while attempting to walk he sways to one side and almost fall." (father 1)

SECTION 2:Facilitating Factors for HT
Theme 4: Goal-directed positive attitude
Parents' Independent Effort and Self-Motivation
Parents are empowered to take over the role of therapist at home. They take the initiative by inventing inexpensive and simple aids and therapy equipment. Parents also said they put in their effort to comply with HT and not depend on outpatient therapy sessions.

"He used to be afraid of loud noises. So,I put some rice in a bottle to shake, to reduce his anxiety towards noise. Then I search online for exercise, I reconfirm the suitability of those exercises with therapist and tried for my son" (mother 8)

Parents reported that they structured an organised schedule for their children to exercise, monitored with a log book, and working parents hired carers to assist their child's in-home therapy. Besides these, parents provide tangible rewards for their children while or after doing exercises.

"we started to have the log book that what are the exercise that he needs to do every day and how many repetitions and how many times. If I cannot do it, the helper do then I would check it from the exercise book where they do the record. I practise giving break forty-five minutes or one hour, where he can play games or watch movie, then rest. Then, after that we continue exercises." (mother 3)

Self-motivation among parents encouraged the incorporation of HT in their daily demands. Most of them expressed their motivation to see improvement in their children.

"Oh, because I have a target that he can walk on his own before he goes to school next year. That's why I'm all out for him." (father 2)

Child's Positive Behaviour
Implementation of HT is easier if the child responds positively. Parents of children above five have noticed that children can accept HT and enjoy it. Older children above nine years showed motivation to perform HT to achieve targeted goals, mainly for physical improvement.

"The factor that motivates me is an effort from my son for exercises. While I do exercise for him I can see he has effort too and he wants to do it too." (father 2)

"He never rejected exercises. When I say whatever he learns in hospital he has to do it at home, he follows. He never gets angry." (mother 5)

"Like my son, he wants to be like his other siblings. He looks at other people and he believe he could do it." (mother 2)

"After doing it for many years, now my daughter do not wait for my instructions. She does exercises by herself as she noticed the improvement. She has the motivation."(mother 1)

Theme 5: External Support System
Family support enhances HT
Several mothers feel fortunate as they have supportive spouses, parents, in-laws, and siblings. While mothers are away, other family members can perform basic exercises for the child. The household chores and therapy responsibilities can be shared. An example of a parent interview goes like this:

"of course, my effort at home and understanding from my eldest son and my husband's understanding doesn't give me all kinds of nonsense work, so I can fully focus on her and I think it's teamwork. It's not just my effort alone." (mother 1)

"his siblings help to monitor his exercises and observe him to avoid any fall or injuries. My older children always support me for his exercises".(mother 2)

Community support
Few parents enrolled in CP support groups. They get motivation and ideas for HT from other parents in the support group. Three mothers also mentioned that encouragement from healthcare professionals regarding the children's achievement during follow-up gives them a boost to continue HT.

"Usually, I am involved with the advocate group for CP children. So, I see these children do achieve improvement in the day to day. So, that's what encouraged me." (mother 6)

"the praises from doctors and nurses, the good words from them, motivate me to continue to do what I do." (mother 1)

Therapists' Teaching Style
Parents in this study give credit to their therapist in the hospital for their goal-orientated intervention. It influences them to perform HT.

"He feels very comfortable with his therapist who has been communicating, talking to him, so he is engaged with her you know. Hence, he is compliant to the homework given by the therapist" (mother 3)

"Each time I bring my son for therapy, she will set the target. So, she will tell me what I should do. Then, when I go to therapy again, she will tell me maybe if we can see improvement or not. If no improvement on that visit, she will add on new therapy and guide me." (mother 10)

SECTION 3: Barriers for HT

Theme 6: Physical health as barrier

Child's Health

Parents are unable to perform HT when their children are not well. Common health issues were infection and seizure, requiring frequent hospital admission. Younger children with severe CP are often tired and sleepy, which also interrupts HT.

"So, one of the things especially for CP child is that whenever they get sick right, that is the time we really, sometimes we say all the effort we put in for one two weeks may have gone you know, then we have to redo over again." (mother 3)

Parents' Health

Every parent in this study juggles multiple chores and often gets tired and low energy. During this time, they need help from other family members or skip the HT. However, two mothers in this study said they skip most of the HT on weekdays as they are exhausted from other house chores and have limited help from family. One of these mothers works, and the other mother is a housewife.

"I'm tired and not being able to care about him, but so far I try, I try my best." (mother 12)

Theme 7: Psychological Health as a Barrier

Parental Psychological Limitation

Parents reported that their mood is affected, and they are under pressure when incorporating HT into their daily routines and commitments. Some felt anxious when the child fell while exercising. On the other hand, some had confidence issues about progressing in HT.

"So, because I do a lot of things, all these things I become frustrated. So, when I do all these things extra work for my daughter, I become easily hot-tempered". (mother 1)

"It's just that I'm worried, he can't even balance his body. Even though we exercise him, but because he can't balance his body, sometimes he falls by himself, just like that". (father 2)

Child's Psychological Limitation

Children with severe CP of GMFC IV to V are unable to comply with HT. They refuse to exercise and become moody.

"Sometimes she doesn't like it when we want to do it for her, and she's mad about that. Certainly like now, she's smart, if we do some exercises for her, if she doesn't like it, she'll push our hands off or she'll cry and scream." (mother 11)

Theme 8: Limited Time

Parents expressed that limited time is a barrier for parents and children to perform HT. Parents had limited time due to various commitments such as work and house chores duty, and their children also experienced limited time after school to be involved in HT.

"So, my main issue is I don't have enough person to help me. Sometimes, I'm busy with cooking and household jobs; so, I can't assign too much time on him…". (mother 10)

"Yes, lack of time because he needs to spend more time on his academics and really like trying to fight with the times that get more time for him to do. Especially now no exercise for him and sometimes we don't even have half an hour time during weekdays for him. And we really see that he's really deteriorates a lot." (mother 3)

Theme 9: Limited External Support System

Lack of Input from Health Care Staff and Support from Family

Parents experienced limitations in progressing HT when junior therapists are appointed for their child as they are unable to provide goal-directed therapy and guidance for home practise. This causes frustration among some parents in this study. Besides that, low confidence level among family members to perform exercises on the children while parents are working poses limitations for the continuation of HT.

"There's no target set. So, I wouldn't know what my weaknesses are. How far my son has achieved. I don't know what the difference is between the last month and the current month. I don't see because there's nobody assessing." (mother 10)

"like my mother-in-law and siblings are a bit scared to do exercise, because afraid of being wrong, afraid of fall." (mother 10)

Limitation in Resources

Most parents raised concerns about the lack of proper exercise tools or equipment at home to perform HT with their children. Besides that, each time the child progresses to the next level of exercises with therapist at hospital, parents are not equipped with sufficient informative materials for home practise.

"There are no manuals, no videos that we can watch as guidance to progress home therapy." (father 3)

"our equipment is limited. So, we use what we have. If it's here at outpatient therapy, there are many equipment, convenient here. Maybe it's not like this at home." (father 1)

DISCUSSION

This is the first study in Malaysia to examine parents' perceptions of their understanding of HT for children with CP and explore associated factors for implementing HT. In recent years, there were no publications even among countries of ASEAN on this topic or issue. It is important to explore the facts on this topic locally to develop further management protocols to keep young practitioners and stakeholders up to date.

In this study, all parents had a similar understanding that HT is a prescription from a therapist to be done at home to achieve the targeted goal. It offers more frequency and intensity, hence reducing the number of visits to the hospital. A study by Iona Novak, on the experience of parents implementing home exercise, found that the parents perceive HT as guidance and teaching from experts to be conducted at home.[13] This reduces their fear of not having regular exercises by experts in hospitals.

In our study, parents perceive HT as doable and persistence provides multiple physical, functional, and psychological benefits. HT improves their confidence and skills to perform exercises on their children and empowers them to monitor their children's progression. Besides that HT optimizes resources like time and money. Similar to findings from previous studies , parents are empowered to play the main role in their children's therapy and the progression of physical and functional outcomes.[11,13,15]

Uniquely, parents in this study reported negative experiences from HT, which includes, fear of regression and fear of injuring the child. Further analysis of mother 2 ,showed the reason for the mother to stop HT temporarily is due to time and health factor, same as the barriers that have been experienced by other parents. In a randomized control trial discontinuation of strength training for 6 weeks showed regression in muscle strength among children with CP.[26] Hence, without consistent practice, even small regressions in muscle tone, strength, or flexibility could accumulate, potentially leading to a more pronounced stiffness or decreased mobility. Next, father 1 felt fear about inducing a fall in his child who is also a mild CP, GMFCS II, and an ambulant. He expressed shallow confidence in performing HT during the interview and appeared apprehensive about eliciting injury to the child. Upon exploring further, this father was not compliant with HT until seeing the child improve during outpatient therapy sessions. Following that he was motivated to perform HT. A randomized clinical trial of 6 weeks of a home strengthening program for 21 children with CP aged 8-18 years old did not report any adverse events.[27] Another randomized controlled trial of a sit-to-stand exercise program that was done at the rehabilitation center and at home only reported fatigue as an adverse event.[28] In other available literature, most parents report fear while their CP children are in school and during other recreational activities, but not during HT.[29-31] Limited data was reported about parents having fear while performing HT.

The pronounced facilitator of HT found in this study was the intrinsic motivation of parents and older children for goal achievement. Upon analyzing further, we found these parents have some similar features. They received structured outpatient visits with frequent reassurance from the therapist, they were portrayed as role models to other parents by healthcare workers, most of them were mothers as main carers, and enhanced with improvement of the children. Standard care of rehabilitation should be enhanced with comprehensive psychological intervention to cultivate motivation to facilitate the implementation of HT. This has been not mentioned as a finding in other similar work.

Barriers found from this study were limited resources,time, external support system, and poor physical and mental health of both parents and child. These local findings are generalized to other previous studies as well.[10-11,13-15] However, the unique perspectives found in this study led parents to propose several valuable recommendations based on their perceived ideas and experiences to overcome those barriers. Standard guidance on initiating exercises and to progress the HT should be provided as written documents or videos to parents. Therapists should be aware of individualized goal-setting according to the children's improvement during each visit. Implementing schemes to loan equipment, conduct home visits, or offer telerehabilitation can facilitate HT and minimize barriers. Regular training and guidance for junior therapists will improve the therapist's teaching style. The government or stakeholders should consider involving non-governmental bodies to enhance the support system for HT for CP children. Some of the suggestions here are very specific to this study and not found in previous literature.

Exploring the relationship between parents, families, and therapists would deepen our understanding of this context. Additionally, involving community, governmental, and nongovernmental stakeholders would help to produce a robust impact. Investigating the perceptions of healthcare workers, therapists, and stakeholders in future studies would provide valuable insights.

LIMITATION

In our study, we are lacking sociodemographic data of participants. Hence further analyses of the negative experiences of parents during HT were limited.

CONCLUSION

Motivation to perform HT was high among mothers in this study. These mothers demonstrated adequate family support and encouragement from healthcare workers. They are compliant with HT juggling all other barriers. The pronounced and well-mentioned intervention will be a comprehensive psychological assessment and support for a successful HT. One-stop patient-centered transdisciplinary care of rehabilitation and pediatric psychologists will enhance the care and compliance to HT.

ACKNOWLEDGMENT

This study is part of the first author's thesis for Master of Rehabilitation Medicine program at University of Malaya, Malaysia. The authors would like to express their gratitude to all participants in the study.

FUNDING

None

CONFLICT OF INTEREST DECLARATION

The authors declare that there was no conflict of interest.

REFERENCES

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D., et al. A report: the definition and classification of cerebral palsy April. Dev Med Child Neurol Suppl 2006; 49(6): 480.
2. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013; 55(6): 509-19.
3. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics 2002; 110(6): 1220-5.
4. Braun KVN, Doernberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. Birth Prevalence of Cerebral Palsy: A Population-Based Study. Pediatrics 2016; 137(1): 1–9.
5. McIntyre S, Goldsmith S, Webb A, Ehlinger V, Hollung SJ, McConnell K, et al. Global prevalence of cerebral palsy: A systematic analysis. Dev Med Child Neurol. 2022; 64(12): 1494-506.
6. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy.Dev Med Child Neurol Suppl 2007; 109: 8-14.
7. Krigger KW. Cerebral palsy: an overview. Am Fam Physician 2006; 73(1): 91-100.
8. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Translational pediatrics 2020; 9(1): 125-35.
9. Novak I. Evidence-Based Diagnosis, Health Care, and Rehabilitation for Children With Cerebral Palsy. Journal of Child Neurology 2014; 29(8): 1141-56.
10. Novak I, Cusick A, Lowe K. A pilot study on the impact of occupational therapy home programming for young children with cerebral palsy. American Journal of Occupational Therapy 2007; 61(4): 463–8.
11. Novak I, Cusick A. Home programmes in paediatric occupational therapy for children with cerebral palsy: Where to start? Autralian Occupational Therapy Journal 2006; 53(4): 251-64.
12. Novak I, Mcintyre S, Morgan C, Campbell L, Dark L, Morton N. et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Developmental medicine & child neurology2017; 55(10): 885-910.
13. Novak I. Parent experience of implementing effective home programs. Phys Occup Ther Pediatr 2011; 31(2): 198-213.
14. Hinojosa J. How mothers of preschool children with cerebral palsy perceive occupational and physical therapists and their influence on family life. Occupational Therapy Journal of Research 1990; 10(3): 144–62.
15. Demeke ZD, Assefa YA, Abich Y, Chala MB. Home-based therapy and its determinants for children with cerebral palsy, exploration of parents' and physiotherapists' perspective, a qualitative study, Ethiopia. PLoS ONE 2023; 18(2): e0282328.
16. Law M, King G. Parent compliance with therapeutic interventions for children with cerebral palsy. Dev Med Child Neurol 1993; 35(11): 983-90.
17. Ryan L, Mulholland J, Agoston A. Talking Ties: Reflecting on Network Visualisation and Qualitative Interviewing. Sociological Research Online 2014; 19(2): 1-12.
18. Suddick KM, Cross V, Vuoskoski P, Galvin KT, Stew G. The Work of Hermeneutic Phenomenology. International Journal of Qualitative Methods 2020; 19: 1-14.
19. Hunt B. Publishing qualitative research in counseling journals. Journal of counseling & development 2011; 89(3): 296-300.
20. Chester K, Whiting L, Spencer N. Understanding young people's experiences and perceptions of relational bullying: a qualitative study. British journal of child health 2023; 4(1): 19-28.
21. Mei C, Reilly S, Reddihough D, Mensah F, Green J, Pennington L, Morgan AT. Activities and participation of children with cerebral palsy: parent perspectives. Disability and Rehabilitation 2015; 37(23): 2164–73.
22. Orb A, Eisenhauer L, Wynaden D. Ethics in Qualitative Research.Journal of Nursing Scholarship 2001; 33(1); 93-6.
23. Birt L, Scott S, Cavers D, Campbell C, Walter F. Member Checking: A Tool to Enhance Trustworthiness or Merely a Nod to Validation? Qualitative Health Research 2016; 26(13): 1802-11.
24. Belotto MJ. Data analysis methods for qualitative research: Managing the challenges of coding, interrater reliability, and thematic analysis. The Qualitative Report 2018; 23(11): 2622-33.
25. Peplow UC, Carpenter C . Perceptions of parents of children with cerebral palsy about the relevance of, and adherence to, exercise programs: a qualitative study. Physical & occupational therapy in paediatrics 2013; 33(3): 285-99.
26. Wang TN, Wu CY, Chen CL, Shieh JY, Lu L, Lin KC. Logistic regression analyses for predicting clinically important differences in motor capacity, motor performance, and functional independence after constraint-induced therapy in children with cerebral palsy. Research in developmental disabilities 2013; 34.3: 1044-51.
27. Dodd KJ, Taylor NF, Graham HK. A randomized clinical trial of strength training in young people with cerebral palsy. Developmental Medicine & Child Neurology2003; 45(10): 652-7.
28. Chaovalit, Sirawee, Karen J. Dodd, Nicholas F. Taylor. Sit-to-stand training for self-care and mobility in children with cerebral palsy: a randomized controlled trial. Developmental Medicine & Child Neurology 2021; 63(12): 1476-82.
29. Lauruschkus K, Nordmark E, Hallström I. Parents' experiences of participation in physical activities for children with cerebral palsy - protecting and pushing towards independence. Disabil Rehabil 2017; 39(8): 771-8.
30. Swaffield E, Yang JF, Manns P, Chan K, Musselman KE. Parents' perceptions of functional electrical stimulation as an upper limb intervention for young children with hemiparesis: qualitative interviews with mothers. BMC Pediatrics 2022; 22(1): 346-31.
31. Elangkovan, Ian Thiruchelvam, and Shefaly Shorey.Experiences and needs of parents caring for children with cerebral palsy: A systematic review. Journal of Developmental & Behavioral Pediatrics 2020; 41(9): 730-73941.9

The efficacy of vagus nerve stimulation for epilepsy in Malaysia

Si-Lei Fong, MRCP[1], Kheng-Seang Lim, PHD[1], Raymond Azman Ali, MMed[2], Hui-Jan Tan, MRCP[3], Ching-Soong Khoo, MRCP[3], Ahmad Rithauddin Mohamed, MRCPCH[4], Choong-Yi Fong, MRCPCH5, Sanihah Abdul Halim, MMed[6,8], Zamzuri Idris, MS[7,8], Jafri Malin Abdullah, MS[7,8], Sangita Dharshini Terumalay, MRCPCH[9], Azmi Alias, MS[10], Suganthi S Chinnasami, MMed[11], Sapiah Sapuan, MMed[12], Nor Azni Yahaya, MRCPCH[13], Sin-Shen Tan, BS[14], Chong-Tin Tan, MRCP[1], Epilepsy Council of Malaysia[15]

[1]Division of Neurology, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia, [2]Department of Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh, Malaysia, [3]Department of Medicine, Faculty of Medicine, The National University of Malaysia, Kuala Lumpur, Malaysia, [4]Department of Paediatrics, Hospital Tunku Azizah, Kuala Lumpur, Malaysia, [5]Department of Medicine and Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [6]Department of Internal Medicine (Neurology), School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia, [7]Department of Neurosciences, School of Medical Sciences and Hospital Universiti Sains Malaysia, Universiti Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia, [8]Brain & Behaviour Cluster, School of Medical Sciences and Hospital Universiti Sains Malaysia, Universiti Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia., [9]Department of Medicine, Subang Jaya Medical Centre, Selangor, Malaysia, [10]Department of Neurosurgery, Tunku Abdul Rahman Neuroscience Institute (IKTAR), Hospital Kuala Lumpur, Malaysia, [11]Department of Neurology, Tunku Abdul Rahman Neuroscience Institute (IKTAR), Hospital Kuala Lumpur, Malaysia, [12]Department of Medicine, Hospital Sungai Buloh, Selangor, Malaysia, [13]Department of Pediatric, Hospital Raja Perempuan Zainab II, Malaysia, [14]LivaNova M Sdn Bhd, Kuala Lumpur, Malaysia, [15]Epilepsy Council Malaysia, Malaysian Society of Neurosciences

ABSTRACT

Introduction: The first vagus nerve stimulation (VNS) implantation in Malaysia was back in 2000, and the implantation rate increased tremendously since 2019. VNS has been used in patients who had persistent seizures despite epilepsy surgeries or were not candidates for epilepsy surgeries. We aimed to study the efficacy of VNS in Malaysia.

Materials and methods: We conducted a retrospective cross-sectional study on the VNS done in Malaysia. We included DRE patients from all age groups who underwent VNS from 1st January 2000 to 31st December 2022. We analysed the efficacy of VNS for patients with at least one year of implantation.

Results: A total of 62 implantations were performed from 2000 to 2022. Most patients (52.5%) had implantation at <18 years old, 54.0% had focal seizures, 34.4% had Lennox Gastaut Syndrome and 23.0% had developmental epileptic encephalopathy. A total of 22.6%, 42.8%, and 63.3% of patients achieve ≥50% seizure reduction at three months, six months, and one-year post-implantation, respectively. At their last follow-up, 73.5% of patients had ≥50% seizure reduction. The majority of responders were at a current intensity of ≥2mA (98.0%) and 81.6% were at a duty cycle of ≥35%. No significant difference was found between responders and non-responders by age at implantation, duration of epilepsy, and seizure type.

Conclusion: VNS is effective for patients with refractory epilepsy in Malaysia with two-third achieving more than 50% seizure reduction at one year and the last follow-up.

KEYWORDS:
Vagus nerve stimulation, epilepsy, Malaysia

INTRODUCTION

Vagus nerve stimulation (VNS) was first reported to be effective in seizure reduction in three drug-resistant epilepsy (DRE) back in 1990.[1] The current implantable device consists of a battery-powered generator with a fine electrode extending from the device and wrapped around the left cervical vagus nerve. The exact mechanism of VNS has been unknown to date. Its neuromodulating effect was presumably due to neuronal desynchronization, hippocampal plasticity, anti-inflammatory changes and alterations in neurotransmitter levels are all possible mechanisms.[2]

Since the United States Food and Drug Administration (FDA) approved its use in focal DRE in patients more than 12 years old in 1997, VNS has been used in patients who had persistent seizures despite epilepsy surgeries or were not candidates for epilepsy surgeries.[3] In Malaysia, the prevalence of lifetime epilepsy was 7.8 in 1,000 population.[4] An estimated 30% of these patients treated with ASMs were DRE.[5] These patients may benefit from this neuromodulation therapy. The first meta-analysis in 2011 showed an average of 45% seizure reduction after VNS with a higher seizure reduction rate of 51% after more than one year of therapy[6] Patients with generalised epilepsy and children could benefit significantly from VNS.[6] When compared to continued anti-seizure medications (ASMs), patients on VNS were able to achieve ≥50% and ≥75% seizure frequency reduction with the odds ratio (OR) of 2.27 and 3.56, respectively.[7] In other Asian countries, in previous studies, VNS has been shown to

This article was accepted: 08 October 2024
Corresponding Author: Kheng-Seang Lim
Email: kslimum@gmail.com

have similar efficacy in adult and paediatric populations.[8-10] Alongside the seizure frequency reduction, VNS has also been shown to improve self-accessed quality of life (QoL), depression and suicidality over time.[9,11]

The first VNS implantation in Malaysia took place in 2000 but it remained underutilised until 2019 when the implantation rate significantly increased. We aimed to study the efficacy of VNS in Malaysia over these 22 years, to guide the future VNS referral, selection and management in our country.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study on the VNS done in Malaysia, since 2000, the year the first vagus nerve stimulation generator was implanted. This was a national multicentre collaborative study, on the initiation of the Malaysian Epilepsy Council. This study was approved by the Malaysia National Medical Research Registry (NMRR) (NMRR-21-1379-57891 (IIR)).

Data collection

We included DRE patients from all age groups who underwent VNS from 1st January 2000 to 31st December 2022, Data was collected by the site investigators, who are the treating neurologists or neurosurgeons, using a standard data collection form. The data collected included (1) basic demographic: age and sex, (2) clinical history of epilepsy: age of seizure onset, aetiology, seizure type, prior epilepsy surgery, (3) VNS implantation details: model, implantation date, age at implantation, duration from onset to implantation, seizure control after implantation at three and six months, and one year, mean seizure reduction and their VNS parameter settings at last clinical follow up. Data collection was performed from 1st September 2022 to 31st December 2022. Subjects' names were anonymised in data collection.

Statistical analysis

We defined responders as patients who experienced ≥ 50% seizure frequency reduction post-implantation. The statistical analysis was performed using the Statistical Package for Social Sciences version 28 (SPSS version 28). Pearson's Chi-Square tests were used to compare the clinical factors between patients who achieved ≥ 50% and < 50% seizure reduction. A p-value of < 0.05 was considered statistically significant.

RESULTS

VNS implantation trend in Malaysia

A total of 62 DRE patients underwent VNS implantation in our country over 22 years, from 2000 to 2022. The number of implantations increased tremendously since 2019 from 1-2 cases per year to 10 cases in 2019 and peaked at 20 cases per year in 2020. Despite the COVID pandemic in 2020, there were 17 and 6 implantations in 2021 and 2022, respectively. (Figure 1) The implanted generators were PulseTM (Model 102), Demi-PulseTM (Model 103) and AspireHCTM (Model 105) from 2000 to 2018. Aspire SRTM (Model 106) has been used since the second half of 2018.

Basic demographics and clinical characteristics

The basic demographic and clinic characteristics of the patients who underwent VNS implantation were summarised in Table I. A total of 52.5% and 49.1% of patients had implantation before and after 18 years old, respectively. Most of the patients were diagnosed with epilepsy for up to 15 years before implantation. A total of 90.2% of patients had implantation for at least one year. Of the seven patients who had implantation for more than 10 years, four had generator replacement, two did not and one was lost to follow-up.

A total of 54.0% of patients had focal seizure type while 45.9% had generalised seizure type. The commonest aetiology was Lennox Gastaut Syndrome (LGS) (38.2%). Eighteen patients (29.5%) were treated with a ketogenic diet before implantation and five (8.1%) had previous epilepsy surgeries. (Table I)

Overall VNS efficacy analysis

In the efficacy analysis, we included cases with at least one-year post-implantation at the time of data collection (n=61) and excluded cases who did not undergo generator replacement when the previous batteries were depleted (n=2), patients who were lost to follow-up (n=1) and those with missing data (n=4). The seizure responses at three, six months and one year are shown in Table II. The number of cases with ≥ 50% seizure reduction gradually increased from three months (22.4%) to six months (42.8%) and at one year (63.3%). A total of 73.5% of patients had ≥ 50% seizure reduction, 28.6% of patients had ≥ 75% seizure reduction and 6.1% reported no change in seizure frequency at their last follow-up. Two patients were seizure-free at their last follow-up. (Figure 2)

VNS stimulation parameters and efficacy analysis

Among those with ≥ 50% seizure reduction at one year, almost all (48/49, 98.0%) patients were at an intensity output of ≥2.0mA (2.0-3.25mA). (Table II). A total of 74.1% of responders at 1 year were at the intensity output of 2 to 2.5mA while 22.6% were at the intensity of 2.75 to 3.25mA. Similar findings were seen among responders at their last follow-up. Most patients (75.0%) were at the intensity output of 2 to 2.5mA. Another 22.2% of responders were at an intensity of 2.75 to 3.25mA. Only one responder remained at an intensity output of <2mA due to increased seizure frequency on an intensity higher than 1.75mA. A total of 92.3% of the non-responders at the last follow-up were at an intensity of 2.0 to 2.5mA. Majority (40/49, 81.6%) were at DC of 35% (Table II).

Responders versus non-responders to VNS

We did not find any statistically significant association between sex, age at the time of implantation, seizure type, duration of epilepsy and VNS parameters using rapid cycling and mean seizure reduction at the last follow-up. (Table III)

DISCUSSION

VNS implantation trend in Malaysia

Our study showed an upward trend in the number of implantations over these 22 years, with an obvious increase in cases since 2019. This positive trend was due to several factors, such as better knowledge among the neurologists for

Table I: Basic demographic, clinical characteristics, and aetiologies of epilepsies of implanted cases (N=61)[a]

Demographic profile	Number of cases (%)
Sex	
Male	37 (60.7)
Female	24 (39.3)
Age at implantation (years)	
Age < 18	34 (52.5)
Age ≥ 18	27 (49.1)
Duration of epilepsy at the time of implantation (years)	
< 5	13 (21.3)
5.1-10.0	14 (23.0)
10.1-15.0	14 (23.0)
15.1- 20.0	11 (18.0)
>20.0	9 (14.8)
Duration on VNS (years)	
Less than 1 year	6 (9.7)
≥ 1 year[b]	55 (90.2)
Median duration on VNS	2.4 (IQR 1.5, 3.5)
Seizure type	
Focal	33 (54.0)
Generalised	28 (45.9)
Aetiology	
Developmental epileptic encephalopathy	
Lennox Gastaut Syndrome (LGS)	19 (31.7)
Other DEE[c]	15 (25.0)
Focal epilepsy	
Structural abnormalitiesd	11 (18.3)
Temporal lobe epilepsy (Unilateral and bilateral)	6 (10.0)
Tuberous sclerosis	1 (1.7)
Malformation of cortical development	3 (5.0)
Post encephalitis	5 (8.3)
Previous treatment	
Ketogenic diet before implantation	18 (29.5)
Previous surgery[e]	5 (8.1)

[a]One missing data, [b]Seven had implantation for more than 10 years, [c]Infantile epileptic encephalopathy, Doose syndrome, Dravet syndrome, infantile spasms, [d]Structural abnormalities: schizencephaly, colpocephaly, gliosis at the eloquent cortex, previous abscess at frontal lobe, [e]One each had an anterior temporal lobectomy and corpus callosotomy, three with missing data

Table II: VNS parameters in cases with implantation duration of more than 1 year (N=49)

	Seizure reduction at 1 year (N=49), n (%)		Proportion of responders (N=49), n (%)	
	≥ 50% (n=31)	< 50% (n=18)	Responders (n=36)	Non-responders (n=13)
Intensity output (mA)				
< 2	1 (3.2)	1 (5.6)	1 (2.8)	0
2.0-2.5	23 (74.1)	15 (83.3)	27 (75.0)	12 (92.3)
2.75-3.25	7 (22.6)	2 (11.1)	8 (22.2)	1 (7.6)
Duty cycle (%)				
16	4 (12.9)	2 (11.1)	3 (8.3)	3 (23.1)
25	2 (6.5)	1 (5.6)	2 (5.6)	1 (7.7)
35	20 (64.5)	12 (66.7)	24 (66.7)	8 (61.5)
≥ 36	5 (16.1)	3 (16.7)	7(19.4)	1 (7.7)

Table III: Comparison of factors associated with seizure reduction at last follow-up (N=49)

	The proportion of responders (N=49), n (%)		p-value
	Responders (n=36)	Non-responders (n=13)	
Sex			
Male	21 (58.3)	8 (61.5)	0.841
Age at time of implantation (years)			
< 18	13 (36.1)	8 (61.5)	0.112
≥ 18	23 (63.9)	5 (38.5)	
Seizure type			
Focal	18 (50.0)	7 (53.8)	0.812
Generalised	18 (50.0)	6 (46.2)	
Duration of epilepsy pre-implantation (years)			
< 5	6 (16.7)	6 (46.2)	0.172
5.1-10.0	7 (19.4)	1 (7.7)	
10.1-15.0	10 (27.8)	2 (15.4)	
15.1- 20.0	8 (22.2)	1 (7.7)	
>20	5 (13.9)	3 (23.1)	
VNS parameters			
Rapid cycling[a]	30 (83.3)	10 (76.9)	0.683

[a] Rapid cycling with off time ≤1.1 minutes and duty cycle < 50%.

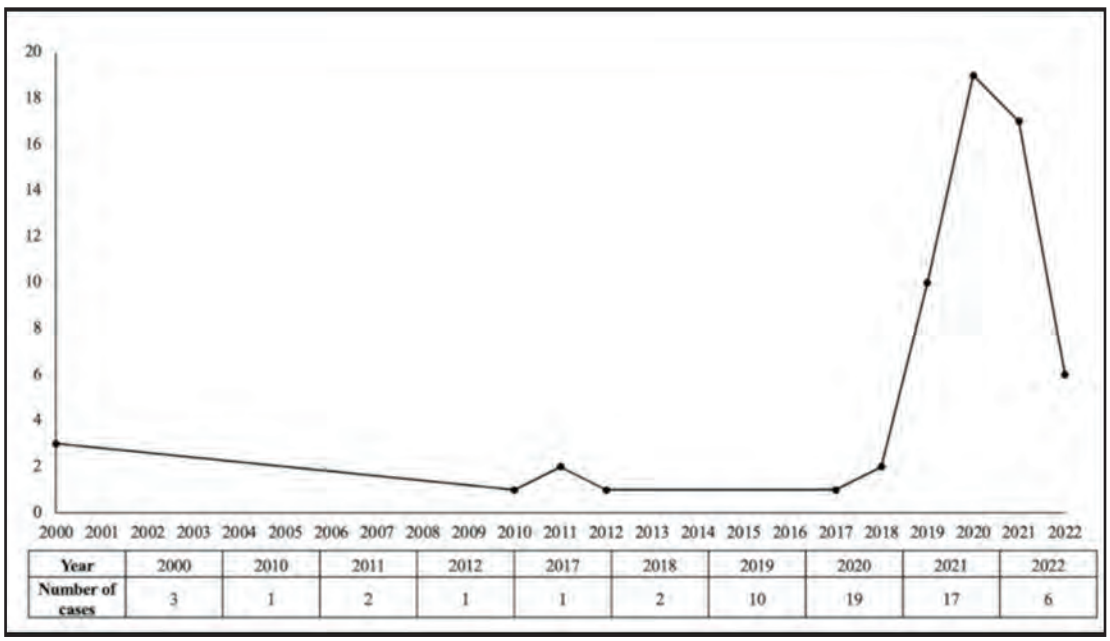

Fig. 1: Number of cases of vagus nerve stimulation implantation over 22 years in Malaysia (N=62)

VNS referral for cases not suitable for resection surgery and a greater number of neurosurgeons who were willing to perform the implantations. In addition, the VNS generator price reduction from USD 22,800 in 2018 to USD 16, 320 in 2019, government subsidization via the National Medical Aid Fund (Tabung Bantuan Perubatan, TBP), public donation for the VNS generators and an increasing number of patients with private insurance were also contributing factors to our increased implantations over the years.

Overall VNS efficacy

The overall VNS efficacy in our cohort was comparable with the efficacy data. VNS efficacy gradually improved over time – 22.4% at 3 months, 42.8% at 6 months and 63.3% at one-year follow-up.[6] Our VNS efficacy at the last follow-up was also similar to the previous meta-analysis in which there were more than half of the patients achieved > 50% seizure reduction.[6] The two paediatric patients who were seizure-free after VNS implantation were Dravet syndrome-like carrying PCDH-19 variant and infantile spasms. VNS were expected to have satisfactory responses in children with DRE of monogenic aetiology especially Dravet syndrome, and tuberous sclerosis complex.[12]

VNS stimulation parameters

Some centres use rapid titration protocol to ensure target intensity output of at least 1.75mA is reached within 3 months post-implantation. Other parameters were adjusted

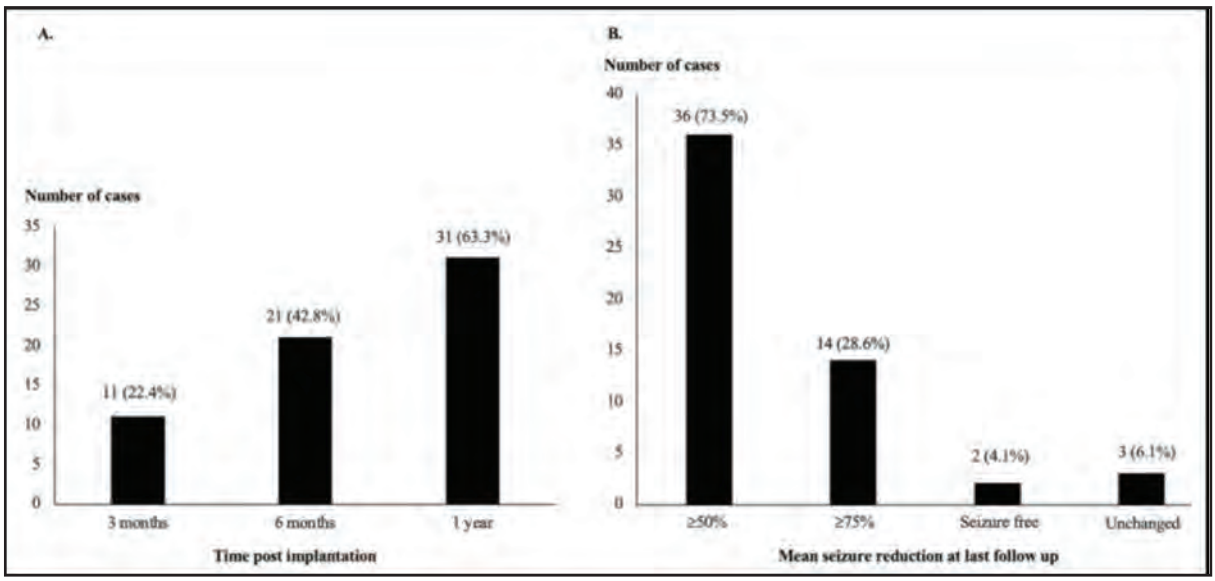

Fig. 2: (A) Time-dependent responders (N=49) and (B) mean seizure reduction rate at last follow-up among patients included for efficacy analysis (N= 49)

to allow better tolerability to this rapid titration (signal frequency 20Hz, pulse width of 250 microseconds) until the target intensity was reached. Rapid titration has been proven to yield faster onset of clinical benefit especially in the paediatric population compared to the conservative titration protocol.[13] This would explain why most of our responders were at the optimal intensity output of ≥2mA.

Challenges of VNS in Malaysia

One of the challenges in the utilization of VNS was the cost of the generator. Although the price reduction has resulted in an increased implantation rate, many patients still require partial subsidisation from the national funds or reimbursement from private insurance to cover the cost. Other patient-related challenges were adherence to the frequent follow-ups during rapid titration in the first three months post-implantation. Since titration could only be done by neurologists in tertiary centres where the implantation was done, the weekly to 2-weekly clinic visits could pose logistic difficulties for some patients, therefore resulting in a suboptimal response from VNS.

Delay in referrals to VNS implantation is another challenge leading to the low implantation rate before 2019. Most patients had VNS surgery done 5 to 10 years after onset of epilepsy. This has also been highlighted in the recent CORE-VNS study, where delays for VNS surgery are common, after multiple trials of ASMs and even failure of epilepsy surgeries, with a median time from diagnosis to first implantation of 10.33 years.[14]

LIMITATIONS

Due to the small sample size, we could not detect a significant difference between responders and non-responders at one year and their last follow-ups to determine the outcome predictors. Future longitudinal studies would be useful to report other findings such as adverse events from implantation and during VNS parameters adjustment, quality of life and long-term efficacy from VNS.

CONCLUSION

Most patients who underwent VNS Malaysia were able to achieve more than 50% seizure reduction at one year and the last follow-up.

CONFLICT OF INTEREST DISCLOSURE

All authors have no conflict of interest to disclose.

REFERENCES

1. Penry JK, Dean JC. Prevention of Intractable Partial Seizures by Intermittent Vagal Stimulation in Humans: Preliminary Results. Epilepsia 1990; 31(s2): S40-S3.
2. Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part II. Headache: The Journal of Head and Face Pain 2016; 56(2): 259-66.
3. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data: Food and Drug Administration; 1997 [Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s207b.pdf.
4. Fong SL, Lim KS, Tan LA, Zainuddin NH, Ho JH, Chia ZJ, et al. Prevalence study of epilepsy in Malaysia. Epilepsy Res 2021; 170: 106551.
5. Fong SL, Lim KS, Khine MY, A Bazir Sherrini,Tan CT. How many more seizure remission can we achieve with epilepsy surgeries in a general epilepsy population? Neurol Asia 2020;25(4):467-72.
6. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg 2011; 115(6): 1248-55.
7. Batson S, Shankar R, Conry J, Boggs J, Radtke R, Mitchell S, et al. Efficacy and safety of VNS therapy or continued medication management for treatment of adults with drug-resistant epilepsy: systematic review and meta-analysis. J Neurol 2022; 269(6): 2874-91.

8. Meng FG, Jia FM, Ren XH, Ge Y, Wang KL, Ma YS, et al. Vagus Nerve Stimulation for Pediatric and Adult Patients with Pharmaco-resistant Epilepsy. Chin Med J (Engl) 2015; 128(19): 2599-604.
9. Kawai K, Tanaka T, Baba H, Bunker M, Ikeda A, Inoue Y, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord 2017; 19(3): 327-38.
10. You SJ, Kang H-C, Kim HD, Ko TS, Kim DS, Hwang YS, et al. Vagus Nerve Stimulation in Intractable Childhood Epilepsy: a Korean Multicenter Experience. J Korean Med Sci 2007; 22(3): 442-5.
11. Kim JS, Kim DY, Jo HJ, Hwang YH, Song JY, Yang KI, et al. Effect of Long-Term Treatment with Vagus Nerve Stimulation on Mood and Quality of Life in Korean Patients with Drug-Resistant Epilepsy. J Clin Neurol 2021; 17(3): 385-92.
12. Xie H, Ma J, Ji T, Liu Q, Cai L, Wu Y. Vagus nerve stimulation in children with drug-resistant epilepsy of monogenic etiology. Front Neurol 2022; 13: 951850.
13. Tzadok M, Verner R, Kann L, Tungala D, Gordon C, El Tahry R, et al. Rapid titration of VNS therapy reduces time-to-response in epilepsy. Epilepsy Behav 2022; 134: 108861.
14. Kwan P, Boffini M, Fahoum F, El Tahry R, O'Brien TJ, Keough K, et al. Baseline characteristics and predictors for early implantation of vagus nerve stimulation therapy in people with drug-resistant epilepsy: Observations from an international prospective outcomes registry (CORE-VNS). Epilepsia Open 2024; 9(5): 1837-46

Exploring alternative approaches to next of kin consenting in the semi-emergency neurosurgical scenario

Erina Natasha Zakaria, MBBS[1], Norli Anida Abdullah, PhD[2,3], Dharmendra Ganesan, MS FRCS (Neuro. Surg)[1]

[1]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, [2]Mathematics Division, Centre for Foundation Studies in Science, Universiti Malaya, Kuala Lumpur, [3]Center for Data Analytics Consultancy & Services, Faculty of Science, Universiti Malaya, Kuala Lumpur

ABSTRACT

Introduction: Prior to any surgical intervention, obtaining informed consent is necessary. In situations where patients are unable to provide informed consent due to mental incapacity or reduced consciousness, the responsibility falls on surrogate decision-makers, typically family members. This predicament commonly arises during neurosurgical emergencies. Various types of surgical emergencies exist, each with its own classification. In cases of life-threatening neurosurgical emergencies and in the absence of next of kin, two consultants have the authority to decide and grant surgical consent. However, for urgent and semi-emergency surgical cases, obtaining consent from the next of kin is crucial. The conventional requirement for the physical presence of the next of kin at the hospital often causes delays in the procedure. This study aims to explore alternative methods for efficiently and compliantly securing this consent for urgent and semi-emergency neurosurgical cases.

Materials and Methods: A prospective, observational cross-sectional survey was conducted from 1st May 2022 to 31st December 2022 at the University of Malaya Medical Centre, Kuala Lumpur. This survey included all neurosurgical patients aged 18 and above requiring urgent and semi-emergency surgery. The next of kin were interviewed using a standardised questionnaire to obtain their perspectives on the effectiveness of the current consenting process, as well as to explore potential alternative methods for obtaining consent. Data were analysed using IBM SPSS Statistics.

Results: The survey had 103 responses. The analysis revealed that the most common semi-emergency surgical procedures were craniotomy (22 cases) and external ventricular drain insertion (18 cases), followed by burr hole and drainage (14 cases). The most common primary diagnosis that needed urgent intervention was acute hydrocephalus. Interestingly, more than half of the patients (58 cases, 56.3%) had to wait for over 30 minutes to obtain consent from their next of kin prior to surgery. The next of kin interviewed had an age range of 25 to 72 years. The relationships of the next of kin were children (33 subjects), spouses (26 subjects), siblings (25 subjects), and parents (16 subjects) of the patients. Additionally, 96.1% of the respondents owned a smartphone with a mobile internet data connection, and 85.4% had internet connectivity at home. The most preferred method of telecommunication for this exercise was via WhatsApp. An interesting finding was the association between the level of trust in medical professionals and the preferred consent method. It was discovered that individuals who preferred physical consent had lower trust in the hospital and doctors, while those who preferred remote consent had higher trust.

Conclusion: The urban Malaysian population are ready to embrace telecommunication for next-of-kin consent in semi-emergency neurosurgical scenarios. These findings form a precursor to further studies to develop algorithms for a secure remote digital surgical consenting platform for urgent or semi-emergency surgical cases.

KEYWORDS:
Semi-emergency, surgical consent, telecommunication, next-of-kin

INTRODUCTION

Informed consent is one of the fundamentals in treating a patient. Consent is the voluntary agreement by a person to the proposal of another; actual willingness that an act or an infringement of an interest shall occur.[1] The doctrine of informed consent is meant to facilitate patient autonomy by allowing patient participation in the medical decision-making process.[2] However, in the event of impaired mental capacity, the decision-making relies on surrogate decision-makers, if available, such as family members. It is legally binding, which is described as "voluntary authorisation, by a patient or research subject, with full comprehension of the risk involved, for diagnostic or investigative procedures and for medical and surgical treatment".[1,3]

In the emergency department, a life-threatening neurosurgical condition would warrant surgery with the agreement of two independent consultants, typically the neurosurgeon and an anaesthetist, without any necessity of patient or family consent. However, in the neurosurgical practice, there are a group of semi-emergency cases which need urgent surgery to prevent deterioration of the condition but are not life-threatening conditions at that material time. The patient might not be able to provide informed consent for an urgent procedure after a failed clinical assessment of competency or due to a reduced consciousness level.[4,5] This group of patients would need informed consent from the next of kin before proceeding with the surgical intervention.[4]

This article was accepted: 17 October 2024
Corresponding Author: Dhamendra Ganesan
Email: dharmendra@um.edu.my

The current practice in our facility is to request for the first-degree family member to physically be present at the hospital to listen to the explanation and obtain written consent. The patient can be wheeled to the theatre for the surgical intervention only after the written consent is obtained. Based on our experience, the need for the physical presence of the next of kin at the hospital at short notice at any time of the day is one of the key reasons that the surgical procedure gets delayed. The delay in arrival could be due to various reasons, such as being engaged at work, having domestic duties, or being caught up in traffic, depending on the time of the day. These circumstances became more challenging during the peri-pandemic period, particularly during the enforcement of the movement restriction order (MCO) at the pandemic's peak. The process of securing written consent in this cohort of patients was significantly delayed, and the hospital policy for the next of kin surgical consenting remained unaltered during the peri-pandemic period. These were some of the predicaments faced during the pandemic phase.

The literature looking at the effects of telemedicine in getting informed consent for remote research study enrolment found no differences in comprehension between telemedicine-based consent and traditional face-to-face methods.6 This method had been adopted during the COVID-19 pandemic by many hospitals, including ours. By using video calls, the surrogate will be able to see the patient, appreciate the severity of the condition, and facilitate decision-making.[7] However, there were limiting factors: limited telecommunication connectivity, availability of suitable devices, privacy and confidentiality.

Unfortunately, despite obtaining verbal consent via telephone, the next of kin was still required to come at some point to physically sign the consent form, as written consent is mandatory for any form of surgical procedure in our hospital policy.

This formed the basis for us embarking on analysing alternative meanings of securing consent for this cohort of patients to find a more efficient means of obtaining the next of kin's consent and ensuring the surgical procedure is carried out in a timely manner. It would only be logical to implement the existing telecommunication methods to execute this process meaningfully and securely. This survey was designed to explore the experience and views of the next of kin regarding the existing process of acquiring consent for surgical treatment and their views and perceptions concerning alternative methods of acquiring consent using digital and media technology.

MATERIALS AND METHODS

An observational cross-sectional prospective study of acquiring informed consent by next of kin for a semi-emergency neurosurgical procedure was carried out between 1st May 2022 and 31st December 2022. The survey was conducted during the pandemic period when the hospital had stringent visiting regulations which limited physical contact between the next of kin and an inpatient family member.

All neurosurgical patients aged 18 years old and above who needed semi-emergency neurosurgical intervention irrespective of the time of the day via consent from the next of kin between the 1st May 2022 and 31st December 2022 at the University Malaya Medical Centre were enrolled in this survey. The universal sampling method was used to collect the sample.

Next-of-kin consent was performed in the standard fashion as per local medical council guidelines. The researcher would obtain the relevant clinical and epidemiology data pertaining to the case from the medical notes.

A questionnaire was framed based on information gathered from discussions with stakeholders, including neurosurgeons, patients and next of kin. The same standard questionnaire was used during all the interviews. The next of kin of the patient was interviewed either in person or through the telephone to get their opinion regarding the process of consenting that had been performed. The questionnaire had a mix of closed and open-ended questions.

Subsequently, bar and pie charts were plotted to display the frequency and percentages of the categorical variables for both patients and next of kin epidemiology, next of kin views on consenting procedure and preference on consenting procedure.

Any obvious dependencies between factors contributing to alternative consenting evidenced from the bar charts would be further investigated using the Chi-Squared test. The null hypothesis for this test is that there are no associations between categorical variables of interest. The relationship between the delay in consenting and proceeding with surgery was also conducted using the Pearson correlation coefficient. Data in this study was analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY).

The survey was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. The study proposal was approved by the Ethics Committee of the University Malaya Medical Centre and the National Medical Research Register (Ethic number 202232-11039).

RESULTS

A total of 130 patients fulfilled the inclusion criteria and were enrolled in this survey. However, there was an attrition of 27 persons; 23 were not keen to continue further, one had a language barrier, and three persons' conditions had deteriorated further and were operated as an emergency with two consultants' consent. In total, 103 responses were analysed. The results of this survey are divided into four parts.

Part 1: Epidemiology

In this survey, a total of 103 patients fulfilling the inclusion criteria were enrolled. The statistical power of the study is 92% at an effect size of 0.4, calculated using the G*Power software.

Table I: Summary of patient's epidemiology

Patient's epidemiology		Number of participants (%)
Race	Malay	32 (31%)
	Chinese	45 (43.7%)
	Indian	24 (23.3%)
	Others	2 (25%)
Gender	Male	72 (70%)
	Female	31(30%)
Type of case	Urgent	53 (51.5%)
	Semi-emergency	50 (48.5%)
Case seen at	Emergency department	76 (73.8%)
	Ward	27 (26.2%)
Diagnosis	Hydrocephalus	25 (24.3%)
	Chronic subdural haemorrhage	16 (15.5%)
	Traumatic brain injury	16 (15.5%)
	Spontaneous intracranial haemorrhage	13 (12.6%)
	Intracranial infection	12 (11.7%)
	Tumoural bleed	6 (5.8%)
	Cerebral infarction	3 (2.9%)
	Spinal trauma	3 (2.9%)
	Others	9 (8.7%)
Procedure done	Craniotomy	22 (21.3%)
	External ventricular drainage	18 (17.5%)
	Burr hole and drainage	14 (13.6%)
	Ventricular peritoneal shunt	10 (9.7%)
	Intracranial pressure monitoring	9 (8.7%)
	Craniectomy	8 (7.8%)
	Wound debridement	8 (7.8%)
	Tracheostomy	3 (2.9%)
	Clipping of aneurysm	2 (1.9%)
	Endoscopic CSF leak repair	2 (1.9%)
	Laminectomy	2 (1.9%)
	Others	5 (4.9%)
Waiting duration for consenting	Less than 30 minutes	45 (43.7%)
	31 – 60 minutes	20 (19.4%)
	61 – 90 minutes	3 (2.9%)
	More than 91 minutes	35 (34%)

The age range of patients enrolled was between 19 and 89 years old, with a median age of 52.2. Their gender distribution was 72 male patients and 31 female patients. The racial distribution was 45 cases of Chinese, 32 cases of Malay, 24 cases of Indian and 2 cases of foreigners (Burmese and Indonesia). Most cases (73.8%, 76 cases) were enrolled at the emergency department, and the remaining (26.2%, 27 cases) were in-patients whose clinical condition eventually deteriorated on the ward. Most emergency cases were cranial conditions, with a small proportion being spine emergencies, as summarised in Table I. In this survey, the commonest emergency surgery procedure was craniotomy (22 cases), external ventricular drain insertion (18 cases), followed by burr hole and drainage (14 cases). A summary of the patient's epidemiology is displayed in Table I.

In our survey, acute hydrocephalus predominates the diagnosis of emergency cases (25 cases) that require urgent intervention, followed by chronic subdural haemorrhage (16 cases), traumatic brain injury (16 cases), spontaneous intracranial haemorrhage (13 cases), intracranial infection (12 cases) as depicted in Table I.

Adapting from the Kulkarni paper on "Pattern and Categorisation of Neurosurgical Emergencies", emergency neurosurgeries can be simplified into life-threatening, organ-threatening or emergent, urgent or semi-urgent.[8] Following this categorisation, certain surgical waiting time limits according to their urgency have been proposed.[8] Our survey defined urgent cases as requiring surgery within 4 hours and semi-emergency as requiring surgery within 72 hours from the time of diagnosis.

Our data collection also captured the duration from obtaining consent from the next of kin and the duration taken to perform the surgery. More than half (61 cases, 56.3 %) of patients is required to wait more than 30 minutes to get consented by the next of kin prior to surgery. Further, a significant moderate linear relationship (correlation coefficient, $R = 0.51$, $p<0.05$) was observed between the delay in obtaining consent and the delay in proceeding with surgery, especially in urgent cases (Figure 1). This suggests that an increase in the time taken to secure consent from the next of kin is associated with a corresponding increase in the time taken to initiate surgery.

Part 2: Next of kin epidemiology

The next of kin age range was between 25 to 72 years old with median age of 45.7 years, with female predominance. They were mainly children (33 subjects), spouses (26

Table II: Summary of the epidemiology and accessibility to digital communication devices and technology by the next of kin

Next of kin epidemiology		Number of participants (%)
Gender	Male	39 (37.9%)
	Female	64 (62.1%)
Relationship	Children	33 (32%)
	Spouse	26 (25.2%)
	Sibling	25 (24.4%)
	Parents	16 (15.5%)
	Others	3 (2.9%)
Level of education	Primary	8 (7.8%)
	Secondary	40 (38.8%)
	Tertiary	55 (53.4%)
Preferable language	Malay	40 (38.8%)
	English	30 (29.1%)
	Chinese	29 (28.2%)
	Tamil	4 (3.9%)
Estimated travelling time to hospital	< 30 minutes	68 (66%)
	31 - 60 minutes	21 (20.4%)
	61 - 90 minutes	2 (1.9%)
	> 91 minutes	12 (11.7%)
Transport to hospital	Own	98 (95.2%)
	Public transport	3 (2.9%)
	Others	2 (1.9%)
Ease of getting to the ward	No issue	81 (78.6%)
	Parking	16 (15.5%)
	Language barrier	4 (3.9%)
	Logistic	2 (1.9%)
	Travelling distance	1 (0.1%)
Type of phone owned	Smart phone	99 (96.1%)
	Basic phone	4 (3.9%)
Other devices ownership	Yes	69 (70%)
	No	34 (30%)
Internet connectivity at home	Yes	88 (85.4%)
	No	15 (14.6%)
Email account	Yes	83 (80.6%)
	No	20 (19.4%)

Table III: Next of kin view on existing consenting process

Consenting process		Number of Patients (%)
Met the treating doctor prior	Yes	61 (59.2%)
	No	42 (40.8%)
Decision for surgery	Need to discuss with other family members before final decision	53 (51.5%)
	One individual decision	50 (48.5%)
Level of understanding regarding surgery	Understood fully and agree	64 (62.1%)
	Understood parts but agree	10 (9.7%)
	Trust the doctor to do what is needed	27 (26.3%)
	Agreed to proceed despite not understanding the operation; however, understood it was urgent	2 (1.9%)
Any concern the consent was taken	Yes	14 (13.6%)
	No	89 (86.4%)
Level of trust in discussion via telephone	Very trust	70 (68%)
	Trust	5 (4.9%)
	Less trust	28 (27.1%)
Consenting without physical presence	Yes	63 (61.2%)
	No	40 (38.8%)
Alternative mode of consent preferred	WhatsApp	80 (77.7%)
	WeChat	13 (12.6%)
	Email	6 (5.8%)
	Phone call	4 (3.9%)

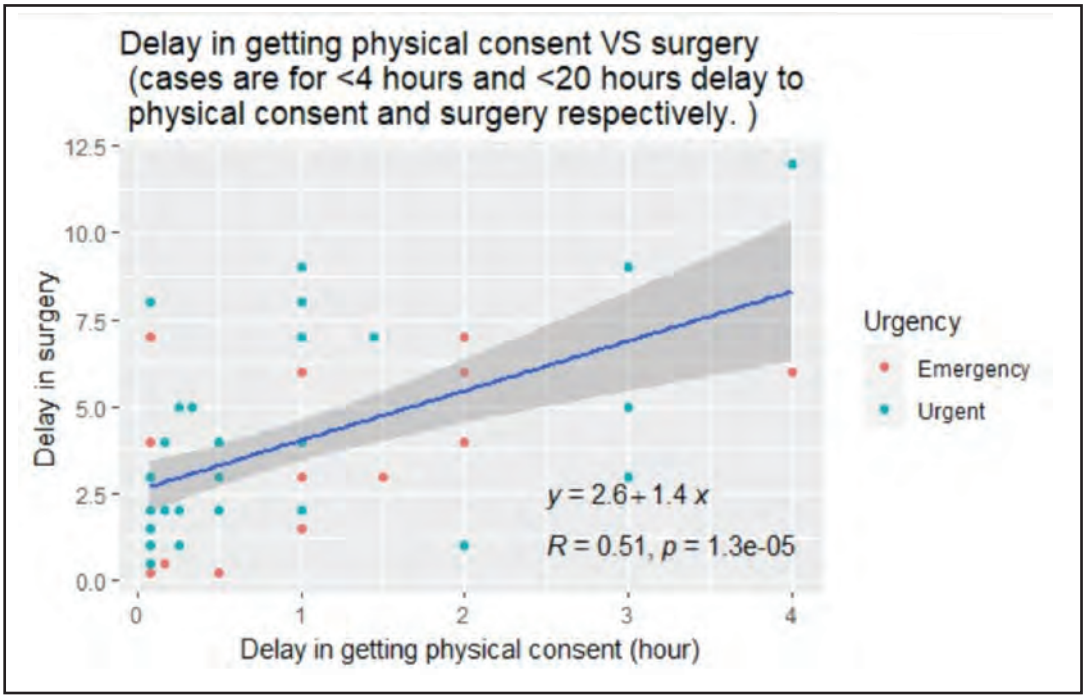

Fig. 1: Scatter plot demonstrating the delay in getting physical consent causing delays in proceeding with surgery especially in urgent cases

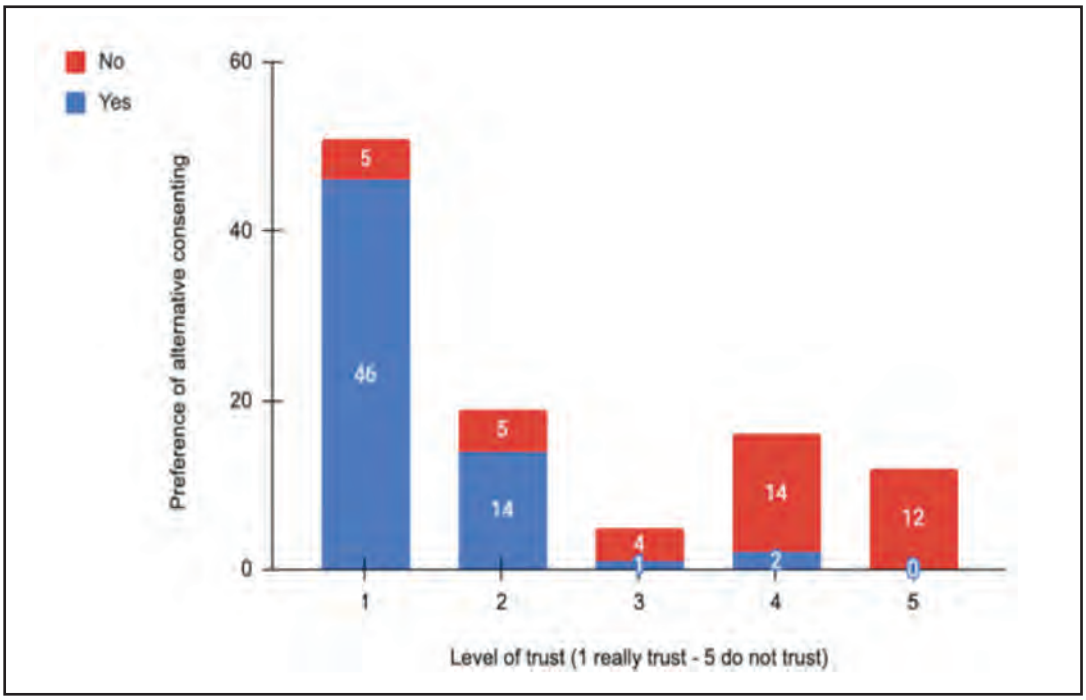

Fig. 2: Association of level of trust in conversation with medical professional via telephone and their view of alternative consenting method, the level of trust linearly increases as their preference of alterative consenting as method of choice

subjects), siblings (25 subjects) and parents (16 subjects) to the patients. The majority have a tertiary education level and prefer to speak in their mother tongues, if possible or either Malay or English as an alternative. The majority stay less than 30 minutes' drive from the hospital (66%, 68 subjects) and have their own mode of transport (95%, 98 subjects).

96.1% of the respondents possessed a smartphone with a mobile internet data connection. 69 subjects (70%) had a computer, laptop or tablet, with 88 subjects (85.4%) had internet connectivity at home. The summary of next of kin's epidemiology is depicted in Table II.

Part 3: Next of kin views on current consenting protocol
The majority of respondents were comfortable with and understood the existing method of consent-taking for urgent and semi-emergency surgery of their next of kin. The survey found that in engagement with the doctor, they would want to be informed about the indication and duration of surgery, risk and possible complications that might occur, recovery period, long-term prognosis and potential improvement of symptoms.

Part 4: Preference on consenting procedure via alternative methods
Most respondents, 61.2%, preferred to give consent without visiting the hospital during the consenting process (Table III); they would have preferred to give their consent via telephone. 38.8% of the participants still wanted to travel to the hospital to sign the papers prior to the surgery. Within the cohort that would not want to be physically present during the consent, 33% preferred to sign the document on another day after they gave their verbal consent through the telephone. The mode of telecommunication most preferred was the WhatsApp application. Summaries on next of kin preference depicted in Table III.

We also found a significant association between next of kin's trust towards medical professionals and their consenting method preference. The respondents who had trust in the hospital and doctors seemed to accept the idea of giving consent verbally via telecommunication, as evidenced by the Chi-Squared test with $p< 0.001$ (Figure 2). Meanwhile, those who preferred to give their consent physically had a lower level of trust in the hospital and doctors.

DISCUSSION

In emergency neurosurgical procedures, time is of the essence. In a survey looking at postoperative mortality in combat traumatic brain injury, it has been concluded that postoperative mortality was significantly lower in patients who underwent craniectomy immediately within 5.3 hours in comparison to a longer delay.[9] In another study to characterise different types of surgical cases to increase the efficacy of surgical timing, many of the neurosurgery emergency cases were classified as level 1 and level 2 priority in tertiary hospitals worldwide.[10] Level 1 emergency cases should be in the theatre within 1 hour, and level 2 cases should be in within 2 hours, indicating the intervention's urgency to obtain a better outcome.[8] Meanwhile, within our local guidelines, emergency surgery is further divided into acute emergency, non-trauma emergency, trauma emergency, urgent and semi-urgent, which carry a different weightage in terms of urgency.[11] The type of surgery can also be classified as immediate life-threatening, life-threatening, organ-threatening, non-critical but emergent, non-critical, non-emergent but urgent and semi-urgent.[8] Therefore, there are various classifications of the type of surgical emergencies and the priority to enter the emergency theatre.

in reality, it is the interaction of the surgeon with the anaesthetist on the urgency of the case and the discretion of the anaesthetist based on the individual case circumstances that are considered in prioritising the operation theatre appropriately. In urgent and semi-emergency cases, one of the factors determining entry to the operation theatre is the written consent for surgery from the patient or next of kin. Our survey revealed an interesting finding: delays in obtaining consent also result in subsequent delays in bringing the patient to the operating room after a case has been booked in the emergency theatre. It is hypothesized that this may be because the anaesthesia team perceives that the consent process has been delayed, leading them to believe that the cases are not as urgent as reported by the surgical team. Based on the survey, this sort of delay could potentially be avoided by utilising advanced telecommunication methods to obtain next-of-kin consent, which in the existing hospital protocol must be done by the physical presence of the next of kin.

The pandemic has stimulated and initiated the need to study the use of digital technology to secure surgical consent from the next of kin in a semi-emergency situation that is robust and aligned with the regulation of the medical council. We foresee this as being the new norm in surgical practice. This concept and framework can later be extrapolated to other areas of consenting in medical practice at large. Noteworthy, the majority of the participants in our survey (61.2%) would consider utilising an advanced telecommunications portal to give informed consent. Therefore, advanced alternative means of communication and consenting in this digital age shows great promise to expedite the patient care in the setting of urgent and semi-emergency surgical cases.

It is evident that 100 % of the next of kin surveyed possess at least one remote communications device, with 96.1% having a smartphone with a mobile internet data connection. The high utility of smartphones is essential for implementing digital consenting in an emergency setting. This allows people to respond promptly from any location without needing to be in front of a computer.

Against this demographic, this survey highlighted that most next of kin (61.2%) would have preferred to consent without visiting the hospital during the consenting process for urgent and semi-emergency cases involving their family member if that option was available to them. The potential reasons for such a response could be that many individuals, due to work commitments, may be unable to leave their jobs suddenly when summoned for emergency consent. Additionally, their close family members may be out of town, it could be late at night, or transportation may be limited. The survey shows that 68% would have complete trust in the discussion, even if it were via the telephone. However, 27% had some trust deficits when engaging in such a discussion via the telephone. The preference appears to be the WhatsApp application, which allows for rapid verbal discussion, video discussion, and messaging without much interruption most of the time. In conclusion, digital telecommunications are a concept that is accepted by the public. A meta-analysis exploring patient satisfaction with the electronic method of the informed consent process showed that they are 1.9 times more satisfied with electronic tools than with the traditional method.[12]

In the post COVID-19 era, many sectors have integrated the latest technology for easy access to different demographics and geographical conditions; for example, there are online classes via virtual classrooms in the education system. Meanwhile, in the healthcare system, multiple applications have been developed to monitor certain conditions, such as cardiovascular care, by monitoring heart rate, rhythm as well as blood pressure monitoring statistics which can be transmitted wirelessly.[13] Furthermore, an e-book has been created to help patients better understand the diagnosis and procedure proposed for certain treatments.[14] Thus, the application of this new technology in health care is becoming more common. Developing an alternative method of obtaining next of kin consent via digital telecommunication is timely for faster treatment in this cohort of patients and convenience for the next kin when contacted any time of the day.

Moreover, 59% of the next of kin had met with the team of treating doctors during the initial admission. Hence, during the consenting process for the urgent procedure, they already had some prior knowledge of the condition and rapport with the doctors in charge. This made the engagement and trust in the telecommunication discussion easier with fewer doubts arising thereafter. This element of trust is key in communication and eases the family's decision-making on behalf of the next of kin. Approximately 51% of the respondents needed extra time to discuss with other family members before deciding. Nevertheless, this is a well-known phenomenon amongst the Asian community as the decision is made by a few key family members in consensus rather than one member alone. Most of the respondents, 62%, understood the discussion points raised and proceeded to give their consent. Meanwhile, 26% signed the consent form based on trust that the doctor would perform what was needed without understanding the details of the procedure.

Trust in medical health care providers is vital for optimum patient-doctor relationships and adherence to the treatment plan given.[15] Thus, it is not surprising that our data has shown an optimistic correlation between the level of trust in telephone conversations and their preference for alternative methods of consenting. Factors contributing to successful communications include politeness, imagination, constructiveness, professionalism, transparency, and technology-friendliness.[16] Other co-factors that determine the information given can be understood, includes social and cultural differences, language inclination, religious beliefs and generation gap.[16] Considering these features, the healthcare providers must be able to describe the clinical conditions in layperson's terms, highlight the relevant information needed and provide the treatment options without bias to make sure the receiver can weigh the pros and cons before making a decision.

Our survey has shown that good communication skills with no language barrier could give confidence to the next of kin in deciding and consenting to the next of kin's urgent or semi-emergency surgery, even though the consultation is not done in a physical face-to-face conversation. However, a point of caution when implementing cutting-edge technologies in the public domain is to ensure those with impairments or who are unfamiliar with technology are not disadvantaged.[12]

The data also corroborates with the results of a study by Ambigapathy R., where it has been found that Malaysian culture is similar to Japanese and other Asian countries' cultures, where shared decision-making is a common practice, collectively done among family members.[17] Approximately 80% of the participants expressed a desire for their spouses to be involved, and over 50% expressed a desire for their children to be included in the discussion.[15] A collective decision is typically taken as the family entity would share in the post-operative care of the next of kin.[17] These points highlight that in many Asian communities, the decision regarding treatment for a next of kin usually involves several family members rather than just one close family member, i.e. spouse or parent.[18] Therefore, the telecommunication engagement of several family members in one sitting may be more fruitful and yield a faster decision than approaching different individuals at different times.

It's important to note that this survey was conducted at a tertiary hospital in an urban setting. Therefore, the findings primarily represented urban sentiments regarding next of kin consenting through telecommunication. It's possible that the demographic of the population may vary in rural areas, and as a result, the survey results may not be directly applicable to rural regions. It's important to remember, nonetheless, that Malaysia has a high level of technical availability, according to the most recent statistics on digital adoption.[19] In Malaysia, there were 33.59 million internet users as of early 2024, which is 97.4% of the country's total population with 129.2% of the population, or 44.55 million active cellular mobile connections, were made.[19] Considering these figures, it is evident that Malaysia possesses the required hardware, internet, infrastructure, and telecommunication connectivity. The focus should be on developing a specific application that addresses the challenges associated with obtaining next-of-kin consent, as revealed in the study.

CONCLUSION

The outcome of this survey highlights that the society of an urban setting in a developing country like Malaysia is prepared and keen to use telecommunication in discussing the consent for the urgent and semi-emergency neurosurgical operation of the next of kin rather than being physically present. This would enable the surgeon to perform the surgery more expediently. The respondents highlight trust in the medical system as a key feature in utilising such technology. These findings form a precursor to further studies to develop algorithms for a secure remote digital surgical consenting platform for urgent or semi-emergency surgical cases.

REFERENCES

1. Malaysian Medical Council Guideline: Consent for Treatment of Patients by Registered Medical Practitioners.
2. Park J, Park H. Surgical informed consent process in neurosurgery. Vol. 60, J Korean Neurosurg Soc 2017; 385–90.

3. Leclercq WKG, Keulers BJ, Scheltinga MRM, Spauwen PHM, Van Der Wilt GJ. A review of surgical informed consent: Past, present, and future. A quest to help patients make better decisions. World J Surg 2010; 34(7): 1406–15.
4. Muskens IS, Gupta S, Robertson FC, Moojen WA, Kolias AG, Peul WC, et al. When Time Is Critical, Is Informed Consent Less So? A Discussion of Patient Autonomy in Emergency Neurosurgery. World Neurosurg 2019; 125: e336–40.
5. Appelbaum PS. Assessment of patients' competence to consent to treatment. N Engl J Med 2007; 357(18): 1834–40.
6. Bobb MR, Van Heukelom PG, Faine BA, Ahmed A, Messerly JT, Bell G, et al. Telemedicine Provides Noninferior Research Informed Consent for Remote Study Enrollment: A Randomized Controlled Trial. J. Acad Emerg Med 2016; 23(7): 759–65.
7. Meneses E, McKenney M, Boneva D, Elkbuli A. Surgical consent during the COVID19 pandemic: Saving lives while in crisis editorial. Vol. 57, Ann Med Surg 2020; p. 163–5.
8. Kulkarni D. Pattern and categorisation of neurosurgical emergencies. J Neuroanaesth Crit Care 2017; 04(04) :S6–8.
9. Wolfe SQ. Developing systems of care: Association of time to craniectomy with survival in patients with severe combat-related brain injuries. Vol. 45, Neurosurg. Focus. AANS; 2018.
10. Ahmed K, Zygourakis C, Kalb S, Pennington Z, Molina C, Emerson T, et al. Protocol for Urgent and Emergent Cases at a Large Academic Level 1 Trauma Center. Cureus. 2019;
11. Ministry of Health Malaysia. (2018). Guidelines: Perioperative Mortality Review – Prioritisation of cases for emergency and elective surgery. Ministry of Health Malaysia.
12. Mirza AB, Khoja AK, Ali F, El-Sheikh M, Bibi-Shahid A, Trindade J, et al. The use of e-consent in surgery and application to neurosurgery: a systematic review and meta-analysis. Acta Neurochir (Wien). 2023; 165(11): 3149–80.
13. Butcher CJ, Hussain W. Digital healthcare: the future. Future Healthc J 2022; 9(2): 113–7.
14. Bethune A, Davila-Foyo M, Valli M, Da Costa L. E-Consent: Approaching surgical consent with mobile technology. Can. J Surg 2018; 61(5): 339–44.
15. Pearson, S. D., & Raeke, L. H. (2000). Patients' trust in physicians: Many theories, few measures, and little data. National Library of Medicine. Available from www.nlm.nih.gov
16. Reddy Bv, Gupta A. Importance of effective communication during COVID-19 infodemic. J Family Med Prim Care. 2020; 9(8): 3793.
17. Ambigapathy R, Chia YC, Ng C J. Patient involvement in decision-making: A cross-sectional study in a Malaysian primary care clinic. BMJ Open 2016; 6(1): e010063.
18. Sekimoto M, Asai A, Ohnishi M, Nishigaki E, Fukui T, Shimbo T, Imanaka Y. Patients' preferences for involvement in treatment decision making in Japan. BMC Family Practice 2004; 5(1): 1.
19. DataReportal. (2024). Digital 2024: Malaysia. Retrieved from https://datareportal.com/reports/digital-2024-malaysia.

Prognostic role of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in critically ill COVID-19 patients: A retrospective study

Wulandari Wulandari, MBBS[1], Muhammad Zulfadli Syahrul, MD[2], Sabrina Ermayanti, MD FISR[3], Zelly Dia Rofinda, MD PhD[4], Elly Usman, PhD[5], Dedy Kurnia, MD PhD[2], Mutia Lailani, MD MSc[6]

[1]Undergraduate Study Program in Medicine, Faculty of Medicine Universitas Andalas, Padang, Indonesia, [2]Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Universitas Andalas/ RSUP Dr. M. Djamil, Padang, Indonesia, [3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Andalas/ RSUP Dr. M. Djamil, Padang, Indonesia, [4]Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine Universitas Andalas/ RSUP Dr. M. Djamil, Padang, Indonesia, [5]Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Andalas, Padang, Indonesia, [6]Department of Physiology, Faculty of Medicine Universitas Andalas, Padang, Indonesia

ABSTRACT

Introduction: Critical coronavirus disease (COVID-19) patients have a high mortality rate. To identify high-risk patients, first-level healthcare facilities can use the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) as prognostic markers. We aimed to assess the NLR and the PLR profile in critically ill COVID-19 patients to predict disease severity.

Materials and methods: This descriptive retrospective study featured 221 patients diagnosed with clinically critical COVID-19 from August 2021 to March 2022 in the Intensive Care Unit (ICU) of RSUP Dr. M. Djamil, Padang, Indonesia. The study employed a total sampling technique to collect data from medical records in the hospital. Patients aged 18 years or older who underwent testing for leukocytes, platelets, neutrophils, and lymphocytes were included in the study. We analysed the data using descriptive univariate analysis. Then, the NLR and PLR of the patients were statistically compared based on comorbidities and coincidence.

Results: According to the study, most patients with critically ill COVID-19 exhibited high levels of NLR (88.2%) and PLR (71.1%). The severe COVID-19 patients with comorbidity of kidney disease had the highest NLR (Mean ± SD) of 31.74 ± 27.95 (p-value <0.001) and the highest mean PLR (Mean ± SD) of 469.33 ± 362.95 (p-value 0.001).

Conclusion: Our findings showed a significantly higher NLR and PLR in patients with critically ill COVID-19, particularly in patients with comorbidity of kidney disease. Thus, elevated levels of NLR and PLR were identified as potential prognostic markers for predicting disease severity in COVID-19 patients, especially those with kidney comorbidity.

KEYWORDS:
Blood test, critical illnesses, hematologic tests, prognostic marker, SARS-CoV-2

INTRODUCTION

Coronavirus disease (COVID-19) is highly contagious and can cause multiple organ failure.[1,2] It has various severity levels, with critical cases requiring life-sustaining therapies.[3] Mortality rates for critically ill COVID-19 patients range from 40 to 67.6%.[4,5] High mortality rates have been observed in critical COVID-19 cases in Indonesia.[6,7] Studies have identified inflammatory biomarkers as predictors of mortality, but unfortunately, lab tests for these biomarkers are not widely available in Indonesia and are only performed in tertiary hospitals.[1,8]

Research has found that Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) levels may impact patients with various conditions, including COVID-19.[9-11] Patients with severe COVID-19 symptoms tend to have higher NLR and PLR levels, indicating a link to mortality.[12-13] Both can be easily measured and are effective predictors of early death in COVID-19 patients.[14]

Research suggests that using a combination of NLR and PLR can improve the accuracy of predicting severity of disease in patients. However, the optimal values for NLR and PLR in predicting disease severity, particularly for patients with comorbidities, require further investigation. Given these considerations, the aim of our study was to determine the profile of NLR and PLR in critically ill COVID-19 patients in the ICU of Dr. M. Djamil Hospital Padang during the delta and omicron eras to predict the disease severity. The data gathered from this study can provide a scientific basis to improve optimal service for critical clinical COVID-19 patients, utilizing minimal infrastructure and preparing for future outbreaks.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary hospital in Indonesia, specifically at the Dr. M. Djamil Hospital in Padang. We evaluated data from 221 patients who were diagnosed with clinically critical COVID-19 and admitted to

This article was accepted: 19 October 2024
Corresponding Author: Mutia Lailani
Email: mlailani@med.unand.ac.id

the COVID ICU during the delta and omicron eras, which were from August 2021 to March 2022. Patient data were collected from electronic medical records at the hospital, and the study was conducted in compliance with the Declaration of Helsinki. The ethical and research committee from the Dr. M. Djamil Hospital, Padang, approved this study with registration number LB.02.02/5.7/273/2023.

Given the retrospective nature of the research, informed consent was waived. The patients included in this study were 18 years or older and tested for leukocytes, platelets, neutrophils, and lymphocytes. We recorded patient characteristics such as age, gender, comorbidities, coincidences, leukocytes, platelets, neutrophils, and lymphocytes while excluding those with incomplete medical records.

Diagnoses were made according to interim guidance from the World Health Organization (WHO). The COVID-19 patients with acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions requiring life-sustaining treatments like mechanical ventilation or vasopressor therapy were considered clinically critical.[3] Age was recorded in years and categorized based on the Ministry of Health of the Republic of Indonesia.[15] Gender was categorized as male or female. Comorbidities were pre-existing conditions that exacerbated the patient's condition, while coincidences were unrelated conditions or events that occurred alongside the COVID-19 infection. These details were recorded in medical records by ICU doctors. The leukocyte, platelet, neutrophil, and lymphocyte count of clinically critical COVID-19 patients were determined by laboratory results from Dr. M. Djamil Padang Hospital during ICU admission. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as follows: NLR = absolute neutrophil count/ absolute lymphocyte count; PLR = platelet counts/absolute lymphocyte count.

The leukocyte count was classified into three groups: normal ($5x10^3$-$10x10^3/mm^3$), leukopenia ($<5x10^3/mm^3$), and leucocytosis ($>10x10^3/mm^3$). Similarly, platelet count was divided into three categories: normal ($150x10^3$ - $400x10^3/mm^3$), thrombocytopenia ($<150x10^3/mm^3$), and thrombocytosis ($>400x10^3/mm^3$). The neutrophil count was classified into normal ($2.5x10^3$ - $7x10^3/mm^3$), neutropenia ($<2.5x10^3/mm^3$), and neutrophilia ($>7x10^3$ mm^3), while lymphocyte count was categorized into normal ($1x10^3$ - $4x10^3/mm^3$), lymphopenia ($<1x10^3/mm^3$), and lymphocytosis ($>4x10^3/mm^3$). These categorizations align with the clinical data interpretation guidelines of the Ministry of Health of the Republic of Indonesia.[16] The NLR values were grouped into normal (<3.13), high (3.13-5), and very high (>5), and PLR values were categorized into normal (≤180) and high (>180), based on previous research.[17] Finally, the NLR and PLR values were described according to comorbidities based on the affected organ system and the coincidence of critical clinical COVID-19 patients in the ICU Dr. M. Djamil Hospital Padang.

In order to mitigate potential biases and ensure the accuracy of our findings, we have taken steps to standardise our sampling procedures and thoroughly review our data for any anomalies or errors. The descriptive univariate analysis will be conducted to identify the frequency distribution characteristics of our research subjects, while the comparison of NLR and PLR values will be analysed using appropriate statistical analysis, i.e., the Anova oneway or Wilcoxon rank-sum test.

RESULTS

In this study conducted from August 2021 to March 2022, 223 patients with clinically critical COVID-19 were initially involved. However, 2 samples (0.9%) had to be excluded due to incomplete medical record data, including age, gender, and comorbidities or coincidences. As a result, the study ultimately included 221 samples. Table I provides detailed information on the characteristics of the participants. The ICU DR. M. Djamil Hospital Padang obtained data for patients with clinically critical COVID-19 in the Delta and Omicron eras. The table showed that 66 patients (29.7%) were aged over 65 years, 112 patients (50.7%) were male, 52 patients (18.7%) had comorbidity of diabetes mellitus, 19 patients (90.5%) were pregnant, 172 patients (77.8%) had leucocytosis, 158 patients (71.5%) had normal platelets, 187 patients (84.6%) had neutrophilia, and 128 patients (57.9%) had lymphopenia (Table I).

According to the NLR and PLR results, most patients with critically ill COVID-19 exhibited high levels of NLR (88.2%) and PLR (71.1%) (Figure 1). The severe COVID-19 patients with comorbidity of kidney disease had the highest NLR (Mean ± SD) of 31.74 ± 27.95, p-value <0.001, and the highest PLR (Mean ± SD) of 469.33 ± 362.95, p-value 0.001 (Table II). In addition, the patients with a coincidence of pregnancy had higher NLR and PLR than those with a coincidence of operation procedures (NLR of 11.63 ± 6.82 vs 3.71 ± 0.50; PLR of 11.63 ± 6.82 and 3.71 ± 0.50 263.20 ± 205.71 vs 220.04 ± 28.70) (Table II).

DISCUSSION

Efficient biomarker tests such as NLR and PLR are known to accurately predict mortality rates in COVID-19 patients. These assessments can be easily administered at primary healthcare centers and have been successfully implemented to diagnose various ailments, including COVID-19.[18] They play a crucial role in managing COVID-19 cases.19 In this retrospective analysis, we evaluated 221 critically ill COVID-19 patients in the ICU at DR. M. Djamil Hospital Padang during the Delta and Omicron periods.

Our findings show that the majority of critically ill COVID-19 patients had significantly elevated NLR levels (>5) and high PLR levels (>180). Interestingly, even those without underlying conditions displayed similarly elevated levels of NLR and PLR when critically ill. Previous research has suggested that NLR could be a potential biomarker for predicting COVID-19 mortality, as evidenced by Violetta et al.[20] In addition, Soumya et al.'s meta-analysis found that PLR was associated with disease severity and mortality in COVID-19 patients, further supported by the findings of Asghar et al., Ok et al., and Wang et al.[21]

In particular, our study identified that a significant proportion of patients with severe COVID-19 were male, over

Table I: Characteristics of Critically Ill COVID-19 Patients in the ICU at DR. M. Djamil Hospital, Padang. The table summarizes the main characteristics of critically ill COVID-19 patients, showing that most were over 65 years old, male, and had diabetes mellitus, leucocytosis, normal platelet counts, neutrophilia, and lymphopenia. Pregnancy was also noted among female patients

PatientçCharacteristics	N (%)
Age	
17-25 years	11 (4,9%)
26-35 years	23 (10,4%)
36-45 years	24 (10,9%)
46-55 years	33 (14,9%)
56-65 years	64 (28,9%)
> 65 years	66 (29,7%)
Gender	
Male	112 (50,7%)
Female	109 (49,3%)
Comorbidities	
Hypertension	31 (11,2%)
Diabetes mellitus	52 (18,7%)
Community pneumonia	17 (6,1%)
Chronic renal failure	28 (10,1%)
Acute renal impairment	24 (8,6%)
Stroke	19 (6,8)
Malignancy	13 (4,6%)
Other cardiovascular disease	26 (9,3%)
Other pulmonary disease	18 (6,5%)
Other neurological diseases	7 (2,5%)
Liver disease	10 (3,6%)
Other diseases	4 (1,4%)
No comorbidities	29 (10,4%)
Coincidences	
Pregnant	19 (90,5%)
Surgery	2 (9,5%)
Leukocytes	
Normal	41 (18,6%)
Leukopenia	8 (3,6%)
Leucocytosis	172 (77,8%)
Platelets	
Normal	158 (71,5%)
Thrombocytopenia	43 (19,5%)
Thrombocytosis	20 (9%)
Neutrophil	
Normal	30 (13,6%)
Neutropenia	4 (1,8%)
Neutrophilia	187 (84,6%)
Lymphocyte	
Normal	92 (41,6%)
Lymphopenia	128 (57,9%)
Lymphocytosis	1 (0,5%)

the age of 65, and had comorbid diabetes mellitus. As shown in Table I, advanced age was closely associated with compromised immunity, reduced physiological function, and a higher prevalence of comorbidities, making elderly patients particularly vulnerable to severe clinical manifestations of COVID-19, which can ultimately lead to increased mortality.[22] Notably, Table I illustrated that males face a disproportionately higher risk of severe COVID-19 compared to females, in agreement with a previous study, mentioning that males are three times more likely to require intensive care unit (ICU) admission and have a 15% greater chance of mortality, as indicated by higher vasopressor levels, prolonged ICU stays, and extended intubation.[23-24] Additionally, a former study found that COVID-19 patients with diabetes mellitus often present with heightened levels of IL-6 and CRP, leading to cytokine storms and systemic inflammation, including acute respiratory distress syndrome (ARDS).[25] Consequently, our findings emphasize that male patients, those over the age of 65, and individuals with comorbid diabetes mellitus are more frequently observed within this critical subset of COVID-19 patients, highlighting the need for targeted interventions in these high-risk groups. Additionally, the majority of patients in this study exhibited leucocytosis, normal platelet counts, neutrophilia, and lymphopenia. Patients with leucocytosis were found to be more likely to have chronic illnesses, experience critical conditions, require ICU admission, receive mechanical ventilation, and face a higher risk of mortality compared to those without leucocytosis.[26] Tessa et al.'s study on platelet index analysis in COVID-19 patients revealed that 73% had normal platelet counts while 20% had thrombocytopenia.[27] Iba et al. also found that patients with severe COVID-19

Table II: Comparison of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) in Severe COVID-19 Patients by Comorbidities and Coincidences. This table shows that patients with kidney disease had the highest NLR and PLR. Furthermore, pregnant patients exhibited higher NLR and PLR compared to those who underwent surgical procedures

Organ-based comorbodities	Neutrophil - Lymphocyte Ratio (NLR)			p-value	Platelet - Lymphocyte Ratio (PLR)			p-value
	Mean	±	SD		Mean	±	SD	
Kidney	31.74	±	27.95	<0.001*	469.33	±	362.95	0.001*
Respiration	21.95	±	20.40		339.28	±	309.85	
Endocrine	20.95	±	14.10		375.25	±	282.55	
Multisystem	20.27	±	18.12		336.70	±	267.28	
Cardiovascular	19.94	±	17.28		289.48	±	195.88	
Malignancy	19.28	±	9.41		314.90	±	131.36	
None	15.17	±	7.06		315.27	±	205.71	
Neurology	11.77	±	8.06		213.21	±	131.72	
Gastrointestinal - Hepatobiliary	10.54	±	8.76		224.51	±	138.79	
Hematology	4.55	±	1.30		149.52	±	60.21	
Coincidences	**Neutrophil - Lymphocyte Ratio (NLR)**			**p-value**	**Platelet - Lymphocyte Ratio (PLR)**			**p-value**
	Mean	**±**	**SD**		**Mean**	**±**	**SD**	
Pregnancy	11.63	±	6.82	0.02**	263.20	±	205.71	0.63**
Operative Procedures	3.71	±	0.50		220.04	±	28.70	

*p-value of Anova oneway test
**p-value of Wilcoxon ranksum test

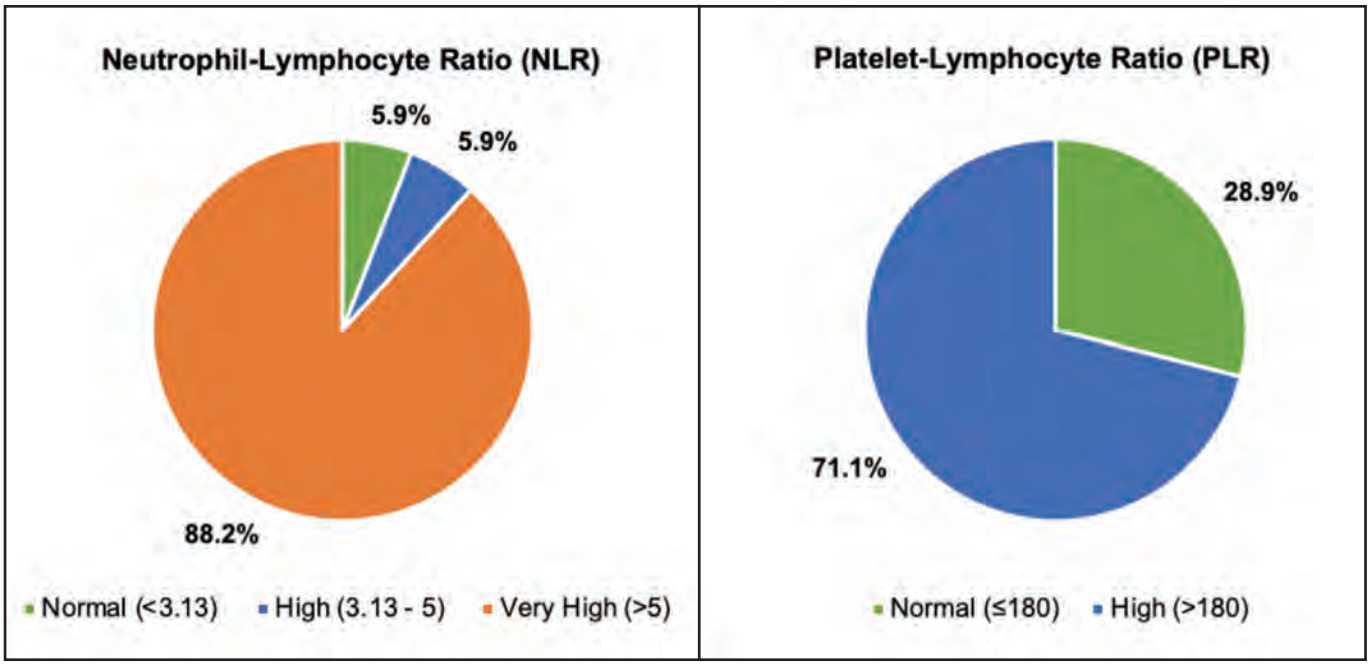

Fig. 1: Proportions of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) Categories (Normal, High, Very High) in Critically Ill COVID-19 Patients. This figure illustrates the distribution of NLR and PLR categories among critically ill COVID-19 patients, indicating that the majority exhibited very high NLR levels and high PLR levels

symptoms often had low platelet and lymphocyte counts.[28] While this study primarily focused on critically ill COVID-19 patients, heterogeneity in the results may have arisen due to differences in patient comorbidities. Platelet counts in COVID-19 patients can be either normal or abnormal, and while no specific theory directly explains normal platelet counts in critically ill COVID-19 patients, it is possible that age, immune response, and the blood clotting process work together to maintain stable platelet levels. Regarding neutrophil counts, Enas et al.'s research demonstrated that neutrophilia and lymphopenia are common hematological changes in critically ill COVID-19 patients, particularly those with cytokine storms.[29]

Our study also explored NLR and PLR values in COVID-19 patients with comorbidities. Notably, patients with kidney disease had the highest NLR and PLR levels among severe COVID-19 cases. According to Arzu et al., COVID-19 patients with chronic renal failure are at a higher risk of severe disease and death. These patients tended to exhibit higher NLR

levels, and those who succumbed to the disease had significantly higher NLR and PLR values than those who recovered.[30] COVID-19 can alter immune responses through various factors such as iron deposition, uraemia, vitamin D deficiency, or haemodialysis, leading to particularly high NLR levels in critically ill patients with kidney disease.[31-32]

In addition, our research identified pregnancy as a common factor among severe COVID-19 cases. Pregnant women had higher NLR and PLR levels compared to those undergoing other medical procedures. Previous studies have suggested that pregnant women are at a greater risk of contracting and experiencing severe symptoms of COVID-19, particularly during the Delta period.[33] Critically ill pregnant patients with COVID-19 are more likely to experience poor prognoses. Recent findings indicate that pregnant women are more susceptible to severe cases of COVID-19 than their non-pregnant counterparts.[34]

However, several limitations must be acknowledged in this study. First, due to the relatively small sample size, NLR and PLR values could not be described in detail based on comorbidities related to specific organ systems, as samples were collected only during a specific time period. Second, this study did not comprehensively review platelet counts in critically ill COVID-19 patients, irrespective of previous therapies. Additionally, limited resources, study scope, and access to patient medical records may have constrained data collection from a larger pool of patients, potentially affecting our understanding of the condition. Future studies with larger patient populations are necessary to establish NLR and PLR cut-off values with optimal sensitivity and specificity before these biomarkers can be implemented in clinical practice.

Nevertheless, this study has notable strengths. The sample was drawn from an Indonesian tertiary hospital population, and the data collection process followed standardized protocols. However, whether the findings from this study can be generalized to other regions remains uncertain, as NLR and PLR values may vary depending on the population being studied. Future research should include multi-centre prospective studies to validate the efficacy of NLR and PLR in predicting disease progression in critically ill COVID-19 patients.

Despite limitations like small sample size and regional focus, our findings provide valuable insights into the prognostic utility of NLR and PLR, warranting further research to validate these results and establish optimal clinical cut-off values.

CONCLUSION

In conclusion, our study underscores the potential of the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as effective biomarkers for predicting mortality in critically ill COVID-19 patients. A significant proportion of our cohort, particularly males over 65 and individuals with comorbid diabetes mellitus, exhibited elevated NLR and PLR levels. Common findings of leucocytosis, normal platelet counts, neutrophilia, and lymphopenia further indicate markers of disease severity. Patients with comorbid conditions, such as kidney disease, showed even higher values, emphasizing the need for heightened monitoring.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

DATA AVAILABILITY

All relevant data related to the manuscript are available upon request from the author.

ACKNOWLEDGMENT

The authors would like to express their appreciation for the ICU and Medical Record team in Dr. M. Djamil Hospital, Padang, Indonesia, who provided data for this research.

REFERENCES

1. Khatib MY, Ananthegowda DC, Elshafei MS, El-Zeer H, Abdaljawad WI, Shaheen MA, et al. Predictors of mortality and morbidity in critically ill COVID-19 patients: an experience from a low mortality country. Health Sci Rep 2022; 17;5(3): e542.
2. Acosta RAH, Garrigos ZE, Marcelin JR, Vijayvargiya P. COVID-19 pathogenesis and clinical manifestations. Infect Dis Clin North Am. 2022; 231–49.
3. World Health Organization. Clinical management of COVID-19: Living guideline. Geneva: World Health Organization; 2023.
4. Costa L, Martins J, Costa M, Oliveira AI, Leal D, Lencastre L. Clinical characteristics and mortality-associated factors in COVID-19 critical patients in a Portuguese ICU. Cureus 2022; 14(9): e29610.
5. Abdi S, Nemati S, Darbaghshahi NN, Mohammadi M, Saeedi E, Naji P, et al. Trends of in hospital and ICU mortality in COVID-19 patients over the fourth and fifth COVID-19 surges in Iran: a retrospective cohort study from Iran. International Journal for Quality in Health Care 2022; 34(3): 1–7.
6. Ariani P, Kurnia D, Meinapuri M, Effendi R, Afriant R, Gustia R. Correlation between C-Reactive Protein level and outcome in coronavirus disease 2019 patients at covid intensive care unit RSUP. Dr. M. Djamil Padang. JAMHESIC 2023; 268–78.
7. Lubis B, Fatoni AZ, Fadhlurrahman AF, Siswagama TA, Vitraludyono R, Lestari MI, et al. Mortality rate of COVID-19 patients in intensive care unit: a multicentre retrospective observational study. J. Med. Chem. Sci. 2023; 6(4): 764–70.
8. Loomba RS, Villarreal EG, Farias JS, Aggarwal G, Aggarwal S, Flores S. Serum biomarkers for prediction of mortality in patients with COVID-19. Annals of Clinical Biochemistry 2022; 59(1): 15–2.
9. Lee M, Lim JS, Kim CH, Lee SH, Kim Y, Hun Lee J, et al. High neutrophil–lymphocyte ratio predicts post-stroke cognitive impairment in acute ischemic stroke patients. Front Neurol 2021; 1(12): 693318.
10. Bedel C, Korkut M. Evaluation of the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and monocyte lymphocyte ratio for diagnosis of testicular torsion. Journal of Acute Disease 2020; 9(5): 13–217.
11. Mouchli M, Reddy S, Gerrard M, Boardman L, Rubio M. Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma. Annals of Hepatology 2021; 22: 100249.
12. Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. J Med Virol 2021; 93(9): 5555–5559.

13. Andiani F, Herawati R, Triyani Y. Correlation between NLR and PLR with the severity of COVID-19 Inpatients. Indonesian Journal of Clinical Pathology and Medical Laboratory 2022; 29(1): 47–53.
14. Nasrani L. Hubungan neutrophil-lymphocyte ratio, absolute lymphocyte count, dan platelet lymphocyte ratio terhadap derajat keparahan COVID-19. Intisari Sains Medis 2022; 13(1): 127–130.
15. Hakim LN. The urgency of the elderly welfare law revision. Jurnal Masalah-Masalah Sosial 2020; 11(1): 43–55.
16. Kementerian Kesehatan Republik Indonesia. Pedoman Interpretasi Data Klinik. Jakarta: Direktorat Jenderal Bina Kefarmasian dan Alat Kesehatan; 2011.
17. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020; 84: 106504.
18. Serban D, Papanas N, Dascalu AM, Kempler P, Raz I, Rizvi AA, et al. Significance of neutrophil to lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in diabetic foot ulcer and potential new therapeutic targets. International Journal of Lower Extremity Wounds 2021; 23(2): 205-16.
19. Lusiantary R. Gambaran rasio neutrofil/limfosit pada kasus preeklamsia. Thesis. http://scholar.unand.ac.id/id/eprint/73495. Accessed on 13 June 2021.
20. Dymicka-Piekarska V, Dorf J, Milewska A, Łukaszyk M, Wiktor Kosidło J, Kamińska J, et al. Neutrophil/Lymphocyte Ratio (NLR) and Lymphocyte/Monocyte Ratio (LMR) Risk of death inflammatory biomarkers in patients with COVID-19. J Inflamm Res 2023; 16: 2209–22.
21. Sarkar S, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: a systematic review and meta-analysis. J Med Virol 2022; 94(1): 211–21.
22. Zimmermann P, Curtis N. Why does the severity of COVID-19 differ with age? understanding the mechanisms underlying the age gradient in outcome following SARS-CoV-2 infection. Pediatr Infect Dis J 2022; 1; 41(2): e36-e45.
23. Chaturvedi R, Lui B, Aaronson JA, White RS, Samuels JD. COVID-19 complications in males and females: recent developments. J Comp Eff Res 2022; 11(9): 689–98.
24. Jirak P, Mirna M, Van Almsick V, Shomanova Z, Mahringer M, Lichtenauer M, et al. Gender-specific differences in the intensive care treatment of COVID-19 patients. J Pers Med 2022; 12(849): 1–10.
25. Findi Z, Indra B, Suharti N, Syahrul MZ, Mulyana R, Yusri E. Hubungan Rasio Neutrofil-Limfosit dengan Derajat Keparahan COVID-19 pada Pasien Diabetes. Jurnal Ilmu Kesehatan Indonesia. 2023; 4(2): 124–30.
26. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021 12; 385(7):585–94.
27. Barrett TJ, Bilaloglu S, Cornwell M, Burgess HM, Virginio VW, Drenkova K, et al. Platelets contribute to disease severity in COVID-19. J Thromb Haemost 2021; 19(12): 3139–53.
28. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost 2020; 18(9): 2103–09.
29. Al-Saadi EAKD, Abdulnabi MA. Hematological changes associated with COVID-19 infection. J Clin Lab Anal 2022 Jan; 36(1): e24064.
30. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Nat Med 2023; 29(2): 334–43.
31. Ozdemir A, Kocak SY, Karabela SN, Yılmaz M. Can systemic immune inflammation index at admission predict in-hospital mortality in chronic kidney disease patients with SARS-CoV-2 infection? Nefrologia 2022; 42(5): 549–58.
32. Cohen G, Hörl WH. Immune Dysfunction in Uremia—An Update. Toxins (Basel) 2012; 4(11): 962–90.
33. Levitus M, Shainker SA, Colvin M. COVID-19 in the critically ill pregnant patient. Crit Care Clin 2022; 38(3): 521–34.
34. Zhao K, Li R, Wu X, Zhao Y, Wang T, Zheng Z, et al. Clinical features in 52 patients with COVID-19 who have increased leukocyte count: a retrospective analysis. Eur J Clin Microbiol Infect Dis 2020; 39(12): 2279–87.

A multicentre, retrospective study of epidemiology and outcome of aplastic anaemia among adult population in Sabah and Sarawak from year 2006 to 2017

Grace Wan Chieng Lee, MRCP (UK)[1], Mei Yee Yeap, MRCP (UK)[2] ,Xin Yee Tan, MRCP (UK)[3], Andy Sing Ong Tang, MRCP (UK)[4], Yoke Fun Ho, MRCP (UK)[5], Kian Boon Law, MSc[6], Shalin Wan Fei Lee, MNSc (UM)[7], Lee Ping Chew, MRCP (UK)[1], Lily Lee Lee Wong, MRCP (UK)[2]

[1]Haematology Unit, Department of Medicine, Sarawak General Hospital, Sarawak, Ministry of Health, Malaysia, [2]Haematology Unit, Department of Medicine, Queen Elizabeth Hospital, Sabah, Ministry of Health, Malaysia, [3]Department of Medicine, Sibu Hospital, Sarawak, Ministry of Health, Malaysia, [4]Department of Medicine, Miri Hospital, Sarawak, Ministry of Health, Malaysia, [5]Department of Medicine, Bintulu Hospital, Sarawak, Ministry of Health, Malaysia, [6]Institute for Clinical Research, National Institute of Health, Ministry of Health, Malaysia, [7]Department of Nursing, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Ministry of Higher Education, Malaysia

ABSTRACT

Introduction: Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with pancytopenia. The annual incidence rates of AA in Asia are observed to be two to three times higher than Europe and North America. Since the introduction of immunosuppressive therapy (IST) and of allogenic stem cell transplant (SCT), the outcome of severe AA has significantly improved. We conducted a 12-year multi-centre retrospective study among the adult AA population in Sabah and Sarawak.

Materials and methods: A total of 119 AA patients had been identified from hospital records of the involved sites, namely Queen Elizabeth Hospital in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from Jan 2006 to Dec 2017.

Results: The median age at diagnosis was 46 years, and native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage of 41.2%, which could be explained by higher frequency of HLA-DRB1*15:01, an alelle linked to increased risk of AA, among this ethnic group. The majority of patients (59.7%) received cyclosporine (CsA) as monotherapy or in combination with other non-IST agents such as danazol, which was instituted in 48.7% of the patients, while a third of them (33.7%) received anti-thymocyte globulin (ATG) therapy with or without CsA, and 12.4% underwent allogenic SCT. The five-year overall survival (OS) for all AA patients was 76.1%. Elderly patients >60 years old and those with severe disease had more inferior 5-year survival.

Conclusion: A prospective study is warranted to determine the true incidence rate, epidemiological distributions, treatment outcome and overall survival of AA patients in Malaysia. Establishment of allogenic SCT in East Malaysia is imperative to make this curative therapy more accessible to patients with severe disease and improve the outcome.

KEYWORDS:
Aplastic anaemia, epidemiology, outcome, Sabah and Sarawak

INTRODUCTION

Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with peripheral blood pancytopenia. The annual incidence rates of AA in Asia, including countries like China, Korea, Japan and Thailand, are observed to be two to three times higher than Europe and North America, where the annual incidence is approximately 2.0 per million population per year.[1] In Malaysia, a retrospective epidemiological study of AA had been conducted in Sabah in the nineties, which revealed significantly higher incidence of AA at 4.8 per million population per year among the South East Asia regions with significant preponderance of the Kadazan-Dusun ethnic group.[2] Although AA has been known to be associated with several aetiologies, including environmental exposure to chemical, medical drugs and viral infections, it has also been linked to genetic susceptibility of certain population to AA.[3] Aplastic anaemia can be life-threatening in its severe form, with early mortality rate at three months as high as 22.6% in the very severe group of a Swedish cohort.[4] However, the outcome has significantly improved with 5-year survival of 70-80% in selected patient cohorts since the introduction of immunosuppresive therapy (IST) and of allogenic stem cell transplant (SCT).[4] In view of the lack of local epidemiological data in AA for the last two decades, this 12-year multi-centre retrospective study was performed to gain a better understanding of the demographic characteristics of AA and to look into real-world treatment outcome among the adult AA population in Sabah and Sarawak.

MATERIALS AND METHODS

A total of 259 adult AA patients had been identified from hospital records and new case registration of the involved sites, including Queen Elizabeth Hospital (QEH) in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from January 2006 to December 2017. All AA patients diagnosed in other hospitals in Sabah were referred to QEH for further management as there was only one haematologist in the whole state of Sabah during the study period, hence captured in the AA registration list at QEH. Ethical approval was obtained from Medical Research

This article was accepted: 05 November 2024
Corresponding Author: Grace Lee Wan Chieng
Email: wanchieng82@gmail.com

and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-18-2160-42948 prior to the start of any study-related activities. Informed consent was not applicable as this was a retrospective study involving data collection which did not involve any investigational product or procedure on the subjects.

Attempts had been made to trace the case notes and clinic folders from Haematology clinic and medical record unit of respective hospitals, and only 119 case notes were retrievable. There were 140 patients (diagnosed in earlier years) from the AA registry of QEH whose case notes were not traceable since QEH was not equipped with central computerised system for clinical notes documentation, hence they were not included in the study. The retrieved case notes were reviewed, and all the relevant information, including patient's demographic details, environmental and occupational exposure to chemicals and toxin, full blood count on presentation, diagnostic bone marrow results, treatment details and outcome, were tabulated into a predesigned case report form. Assessment of exposure to chemicals and toxins, such as solvents and pesticides, was done by history taking from patients or family members. Diagnostic bone marrow aspirate and trephine biopsy reports were traced from the central pathology laboratory of Queen Elizabeth Hospital and Sarawak General Hospital, which handle all the bone marrow trephine specimens from the whole state of Sabah and Sarawak respectively, and reviewed to confirm the diagnosis of AA. Aplastic anaemia is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis with at least two of the following: haemoglobin concentration (Hb) <10 g/dL, platelet count <50 x $10^3/\mu$L, neutrophil count <1.5 x 10/μL. Disease severity was classified according to modified Camitta criteria as followed:[5]

1. Severe AA (SAA): Marrow cellularity <25% (or 25-30% with <30% residual haematopoietic cells), plus at least two of: (i) neutrophils <0.5 x$10^3/\mu$L, (ii) platelets <20 x$10^3/\mu$L (iii) reticulocyte count <20 x$10^3/\mu$L (<60 x$10^3/\mu$L for automated reticulocyte counting)
2. Very severe AA (VSAA): As for SAA but neutrophils <0.2 x$10^3/\mu$L
3. Non-severe (NSAA): AA not fulfilling the criteria for SAA or VSAA

Outcome assessment was done at one year, three years and five years from the date of diagnosis, which was based on response criteria from 'Guidelines for the diagnosis and management of adult aplastic anaemia' of British Society for Haematology 2016:[5]

(a) Response criteria in severe/very severe AA

- None (NR)
  Still fulfil severe disease criteria
- Partial (PR)
  Transfusion independent
  No longer meet criteria for severe disease
- Complete (CR)
  Haemoglobin concentration normal for age and gender
  Neutrophil count >1.5 x$10^3/\mu$L
  Platelet count >150 x$10^3/\mu$L

(b) Response criteria for non-severe AA

- None (NR)
  Blood counts are worse, or do not meet criteria below
- Partial (PR)
  Transfusion independence (if previously dependent) or doubling or normalization of at least one cell line or increase of baseline:
  - Haemoglobin concentration of >3 g/dL (if initially <6)
  - Neutrophils of >0.5 x$10^3/\mu$L (if initially <0.5)
  - Platelets of >20 x$10^3/\mu$L (if initially <20)
- Complete (CR)
  Same criteria as for severe disease

Patients with congenital or secondary bone marrow failure due to chemotherapy or radiotherapy, hypoplastic MDS and patients of age 12 years and below at the time of data collection were excluded from the study.

Demographic characteristics of patients were summarised using descriptive statistics, such as median for numerical variables, frequency and proportion for categorical variables, which were presented in tables. Association of different treatment modalities to disease outcomes was assessed using Pearson's Chi-square test at 0.05 significance level. Overall survival (OS) was defined as the time taken from confirmation of diagnosis to death from any cause or last follow-up. Mortality was confirmed through hospital certification of death or National Registration Department (JPN). Patients who were alive or lost to follow-up were censored. The OS rates were calculated using Kaplan-Meier (KM) method for three months, one year, three years and five years. Differences in OS between groups were compared and tested using the Log-rank test at 0.05 significance level.

RESULTS

Epidemiological characteristics

A total of 119 adult patients with confirmed diagnosis of AA had been identified over the 12-year study period, with 82 patients from Sabah and the remaining 37 from Sarawak. The number of AA cases retrieved in each year from 2006 to 2017 for Sabah and Sarawak is represented in Figure 1. Female preponderance was observed among the AA patients in this cohort, with a male-to-female ratio of 1:1.64. The median age at diagnosis was 46 years, and the majority of patients were from the late middle age group 40-59 years (37.8%, n=45), followed by young adult group 19-39 years (31.9%, n=38) (Table I). Native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage 41.2% (n=49), followed by Malay and Bajau, who both recorded 10.9% (n=13) respectively, while Iban had the highest percentage 7.6% (n=9) among the other Sarawak indigenous groups.

Clinical characteristics

Analysis of the clinical characteristics of AA patients revealed that the lowest median pre-transfusion haemoglobin upon presentation was 5.95 g/dL, white blood count (WBC) 2.3x10^3/uL, absolute neutrophil count (ANC) 0.6x10^3/uL and platelet 7x10^3/uL for all severity groups. About half of the patients (n=61) were classified as having severe AA upon presentation, while 23.5% (n=28) had very severe AA. In the

Table I: Demographics of Aplastic Anaemia patients (n=119)

Variables	N	(%)	Age at diagnosis Median
All	119		46 years
Age groups at diagnosis			
13 – 18 years	12	(10.1)	
19 – 39 years	38	(31.9)	
40 – 59 years	45	(37.8)	
60 and above	24	(20.2)	
Gender			
Male	45	(37.8)	31 years
Female	74	(62.2)	51 years
Ethnic groups			
Kadazan-Dusun	49	(41.2)	47.0 years
Malay	13	(10.9)	42.0 years
Bajau	13	(10.9)	28.0 years
Chinese	12	(10.1)	57.0 years
Iban	9	(7.6)	42.0 years
Bidayuh	4	(3.4)	48.5 years
Rungus	3	(2.5)	29.0 years
Others	15	(12.6)	

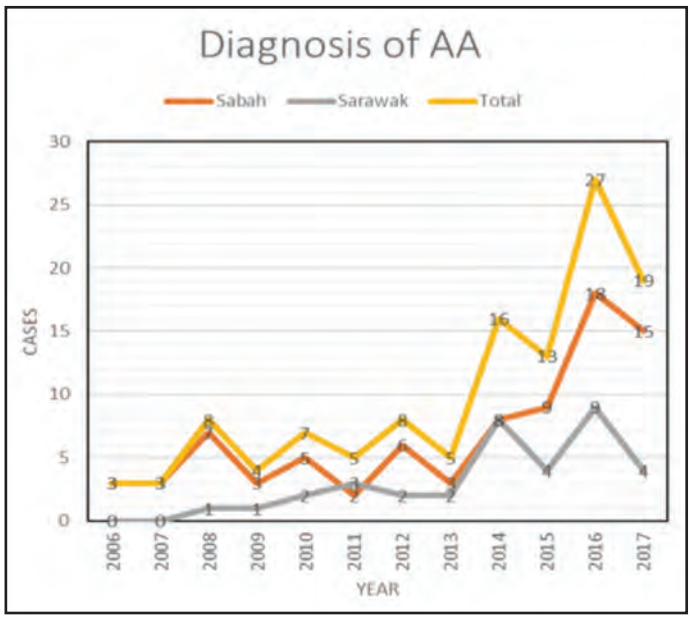

Fig. 1: Number of aplastic anaemia cases retrievable in Sabah and Sarawak from year 2006 to 2017 (n=119)

SAA category, patients aged between 40 and 59 years recorded the highest number of 23/61 (37.7%), followed closely by 22/61 (36.1%) patients from the young adult age group 19-39 years (Figure 2). It was also observed that a total of 39 patients (43.8%) from SAA and VSAA groups were from the transplant-eligible age group of below 40 years old. 19.3% of this cohort (n=23) were elderly patients aged 60 years and above, and 17 of them had severe and very severe disease.

Treatment

Among the SAA and VSAA patients (n=89), only 11 of them (12.4%) underwent allogenic SCT as curative treatment, while those who were not transplant-eligible (33.7%, n=30/89) received anti-thymocyte globulin (ATG), mostly in combination with CsA, as immunosuppressive therapy. Patients who underwent allogenic SCT and received ATG therapy were from the younger age group, with the median age at diagnosis 26 years and 32 years respectively. More than half of the patients from all severity groups (59.7%, n=71) had received cyclosporine (CsA), either as single-agent IST or in combination with other non-IST agents. 24 patients (20.2%) who were unable to tolerate or failed to respond to CsA had also received other IST agents, including mycophenolate mofetil (MMF) and tacrolimus, as the second-line treatment. Two non-IST agents, namely danazol and eltrombopag, were also used across all severity groups, with danazol being instituted in almost half of the patients (48.7%, n=58) patients, and eltrombopag in only 4 patients.

Outcome

Patients with NSAA, who all received non-ATG oral therapy,

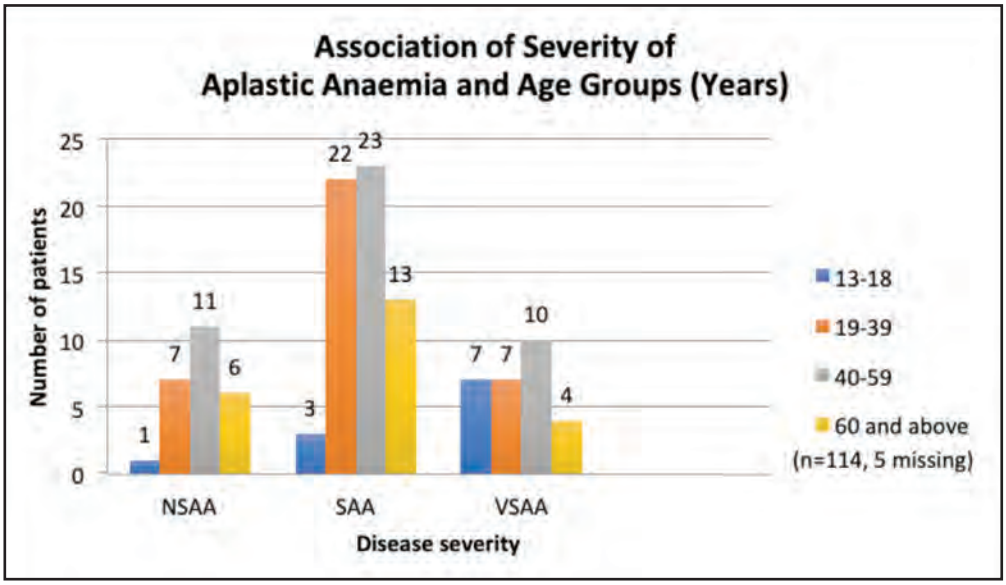

Fig. 2: Number of aplastic anaemia cases in different age groups according to disease severity (n=114, 5 with missing severity data)

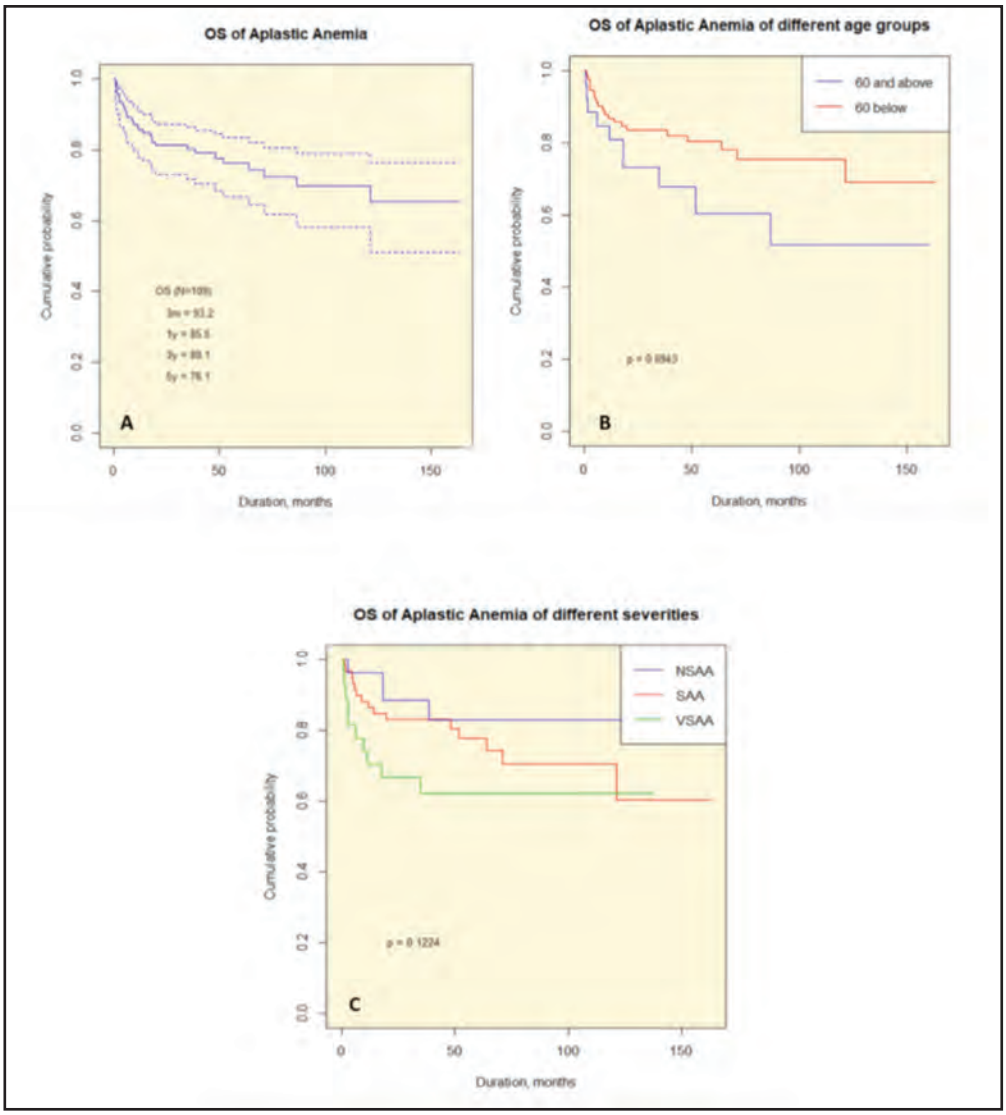

Fig. 3: A) Overall survival at 3 months, 1 year, 3 years and 5 years; B) overall survival by age group below and above 60 years; C) overall survival by disease severity

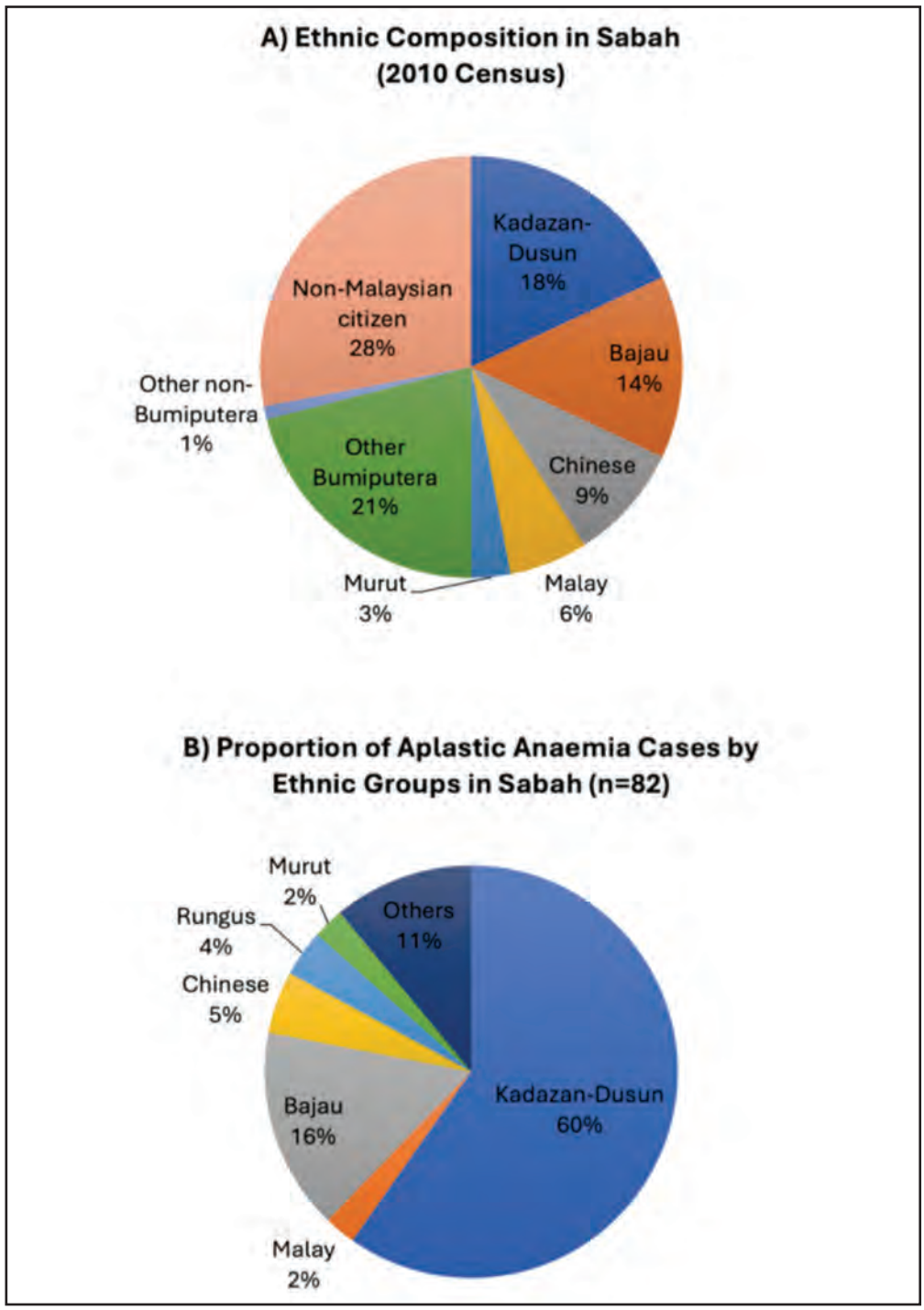

Fig. 4: A) Ethnic composition in Sabah according to Malaysian population census 2010; B) Proportion of aplastic anaemia cases by ethnic groups in Sabah (n=82)

demonstrated an overall response rate of 75% (complete response, CR 16.7% and partial response, PR 58.3%) with a lower mortality rate of 16.7% compared to those with severe disease. In the SAA and VSAA groups, the CR rates were 24.6% and 25% respectively, and the mortality rates were observed to be higher at 24.6% for SAA and 39.3% for VSAA patients in our cohort. Of the 11/89 patients (12.4%) with SAA and VSAA who had undergone allogenic stem cell transplant, 9 of them achieved complete response (CR), while 2 deaths were observed due to upper gastrointestinal haemorrhage and undetermined cause. The remaining non-transplanted patients in these both severity groups had poorer outcome, with 40.3% (n=31) of them demonstrating no response or death. Patients who were not transplant-eligible were analysed according to ATG and non-ATG treatment group, and it was found that there was no significant difference in the treatment outcome in terms of CR rate (20% and 24.6%) and PR rate (40% and 38.6%) (p=0.887). In the non-ATG treatment group, outcome was not assessed according to individual IST and non-IST groups due to treatment heterogeneity.

Survival

The median follow-up duration was 45.8 months, with a total of 31 deaths during follow up. The three-month, one-year, three-year and five-year overall survival (OS) for all AA patients was 93.2%, 85.5%, 80.1% and 76.1% respectively (Figure 3A). Patients in the elderly age group >60 years were observed to have a dismal outcome, with five-year OS of only 60.3% compared to patients <60 years (80.3%) (p=0.0943) (Figure 3B). Further analysis of patients aged below 60 years showed an overall trend of a better outcome in the younger age groups although not achieving statistical significance (p=0.2). There was no significant difference in OS between male and female genders (p=0.40). Patients with VSAA were observed to have the lowest 5-year OS of 62.2%, compared to those with SAA (77.6%) and NSAA (82.9%) (p=0.12) (Figure 3C). Among the patients who had severe disease and were not transplant-eligible, the 5-year OS rate of SAA patients who received ATG treatment was observed to be higher (93.3%) compared to the non-ATG treatment group (79.4%), although this was not statistically significant (p=1.0). The 3-year OS rate of VSAA in the ATG treatment group (64.3%) also appeared to be superior compared to the non-ATG treatment group (42.9%) despite lacking statistical significance (p=0.40).

DISCUSSION

The frequency of newly-diagnosed aplastic anaemia cases has been observed to be significantly higher in the state of Sabah than any other parts of Malaysia. An epidemiological study of AA in Sabah by Yong et al (2) in the nineties revealed an annual incidence rate of 4.8 per million population, which was higher than that of other South East Asian countries.[2] Since then, there is lack of epidemiological or outcome data on AA in Malaysia, which prompted us to embark on this retrospective study to gain more understanding in the epidemiology and outcome of AA in Sabah. We also included the state of Sarawak as Sarawak is situated on the Island of Borneo which may share similar ethnicities and cultural behaviour as its neighbour Sabah. Hence it would be interesting to explore if there was any difference in the AA epidemiological and outcome data of both states.

From the data collected, it was observed that the number of new cases diagnosed in Sabah each year had been consistently higher than that in Sarawak, and the total number of cases recorded in Sabah over the 12-year period of this study (n=82) was more than twice higher than that recorded in Sarawak (n=37). The population of Sabah from Malaysian Census 2010 was reported as 3.21 million, ranking the third among other states and was slightly more populous than Sarawak, which reported a population of 2.47 million in the fourth place.[6] However, the incidence rate was not analysed as slightly over half of the case notes of the patients from the Sabah AA registration list were not retrievable, hence rendering the incidence rate to be under-reported if it were to be analysed. This is a major limitation of this retrospective study, as most of the hospitals in the state of Sabah and Sarawak still rely on manual documentation of clinical notes, except for Bintulu Hospital in Sarawak, and many of the initial volumes of case notes containing diagnostic clinical and laboratory information were not retrievable, especially for patients who were diagnosed in the earlier years of this study period.

Another interesting demographic finding is that the native ethnic group of Kadazan-Dusun from Sabah was observed to be of the largest proportion (41.2%) of the total AA cases (Figure 4B). In comparison to the percentage of the Kadazan-Dusun in Sabah population, which was only 18% according to the 2010 Malaysian census (Figure 4A),[6,7] the percentage of AA cases diagnosed among the Kadazan-Dusun in Sabah was disproportionately higher at 59.8%. This striking finding is better depicted when the calculated incidence of AA among the Kadazan-Dusun revealed an incidence rate of 113.1 per million population compared to only 16.7 per million population among the non-Kadazan-Dusun AA patients in Sabah. Similar observation had been reported by Yong et al, who also found the Kadazan-Dusun to represent a large proportion of 77% of their AA study cohort in Sabah.[2] A genetic study performed by Institute for Medical Research, Malaysia in 2010 among the Kadazan-Dusun AA patients and genetically-matched controls in Sabah had demonstrated that there was increased frequency of HLA-DRB1*15:01 among the Kadazan-Dusun, and this allele was significantly associated with AA.[8] In another meta-analysis by Liu et al in 2016, it was concluded that HLA-DRB1*15 and HLA-DRB1*15:01 polymorphism were potential risk factors for AA in the majority of the studies,[9] which could probably explain the increased incidence of AA among the Kadazan-Dusun ethnic group.

In recent years, a few population-based studies have demonstrated that age is one of the prognostic factors which determines the survival rate in AA patients. In a Sweden AA study in 2000-2011, the five-year OS of AA patients aged above 60 years was significantly lower (38.1%, p=0.001) compared to those aged between 40-59 years (70.7%, p=0.029), and Taiwan nationwide population AA study (2001-2010) demonstrated similar inferior five-year OS in patients above 60 years old (38%, p=<0.001) compared to patients aged between 40-59 years (60.9%).[4,10] Patients aged above 60 years from our study cohort were also observed to have more inferior five-year OS (60.3%) compared to those below 60 years (80.3%), although not statistically significant (p=0.094). Among all the severity groups, patients with severe disease were also observed to have poorer outcome (Figure 3C), with VSAA group doing the worst. Other population studies in Sweden, Taiwan and China have also demonstrated similar trend of OS according to disease severity.[4,10,11]

Despite the dismal outcome in patients with severe aplastic anaemia, long-term survival can be achieved in a major proportion of the patients with the advent of allogenic stem cell transplantation and immunosuppresive therapy as the definitive treatment.[12] In patients younger than 40 years with HLA-matched sibling donor, stem cell transplant should be the first-line therapy.[13] In this study cohort, there were 39 patients with SAA and VSAA younger than 40 years old, but only 11 patients underwent allogenic SCT. Inavailability of HLA-matched sibling donor was likely one of the reasons that some of the remaining 28 patients were not transplanted. In

addition, logistic and financial issues were also among the compounding factors that hindered patients from the East Malaysian states to travel all the way to Ampang Hospital in West Malaysia, which is the referral centre for Sabah and Sarawak for allogenic stem cell transplant. Since the survival outcome of SAA and VSAA had been shown to be more inferior compared to NSAA, and a significant proportion (43.8%) of patients with severe and very severe disease in this cohort were aged younger than 40 years, more patients should be aimed for allogenic stem cell transplant as the first-line treatment if HLA-matched sibling donor is available. The establishment of allogenic stem cell transplant service in Sabah and Sarawak will likely be able to overcome the logistic issues as mentioned earlier and increase the opportunities of patients being cured of this potentially fatal disease. In the absence of matched sibling donor, matched unrelated donor transplantation, which is offered in Ampang Hospital, can also be considered in younger patients who fail first-line immunosuppresive therapy.[13] First-line immunosuppresive therapy (IST) usually consists of horse or rabbit anti-thymocyte globulin (ATG) in combination with cyclosporine for patients with severe disease, with a response rate of 60-80%.[14] Of 89 patients with SAA and VSAA in this study, only 30 patients (33.7%) received ATG and cyclosporine as the first-line IST. More than half of the patients with severe disease (53.9%) did not receive ATG and were treated with cyclosporine with or without danazol. Due to vast geographical factor, many AA patients in Sabah and Sarawak presented late to the nearest healthcare facilities in critically ill condition with neutropenic sepsis, hence rendering them unfit for ATG as the initial IST. In addition, elderly patients above 60 years old, who constituted 19% of the SAA and VSAA groups, were generally the frailer group and at higher risk of acute and delayed toxicities of ATG-based treatment, resulting in lower ATG uptake as IST among patients with severe disease.

Several limitations had been identified in our study, and one of them was the retrospective study design, in which data collection process was hindered by lack of central or computerised data storage and effective data tracing system in the involved sites. From the total 259 AA patients identified, 222 patients were obtained from QEH AA registration list from year 2006 to 2017, but only 82 case notes were retrievable and the remaining 140 were unaccounted for. The majority of the unretrievable case notes belonged to patients diagnosed in earlier years and those who were deceased or no longer under active clinic follow up. 37 AA patients were identified from the hospital sites in Sarawak via manual tracing of case note filing and clinic registration book. However, there is still a possibility that some deceased AA patients diagnosed in the earlier years were not captured due to manual tracing method. Failure to trace the case notes of slightly more than half of the total patients identified (54%) is a major limitation to the study, resulting in our inability to accurately report the incidence rate of AA among adult population in Sabah and Sarawak. Nevertheless, the number of AA cases in Sarawak had been observed to be lower compared to Sabah over the years of study period. Other epidemiological data, including occupation and exposure to chemical toxins, were largely missing for many patients due to the retrospective nature of the study, and hence not analysed and reported. Although AA can be part of the disease spectrum of paroxysmal nocturnal haemoglobinuria (PNH), there was lack of PNH data for analysis as PNH screening test was not readily available in Sabah and Sarawak during the study period. Other limitations include small sample sizes for treatment subsets and number of deaths, which might have resulted in lack of sufficient statistical power to detect significant differences. There was also likely selection bias in view of the heterogeneity of our patients and long treatment period with a variety of treatment and supportive care modalities. In patients with severe disease who were not transplant eligible, a selection bias would be expected to occur in those who were younger and fitter for ATG treatment, and a proportion of those who were elderly or unfit would have either succumbed to the complications of severe AA or excluded from ATG treatment.

CONCLUSION

Although Sabah and Sarawak are located on the same Borneo Island, a significantly higher frequency of aplastic anaemia cases among the adults is observed in Sabah compared to Sarawak, particularly among the native Kadazan-Dusun ethnic group, who are likely to be genetically susceptible to the disease. Advanced age above 60 years and severe disease are likely associated with inferior outcome. Despite the dismal outcome in patients with severe aplastic anaemia, long-term survival can be achieved in a major proportion of the patients with the advent of allogenic stem cell transplantation and immunosuppresive therapy as the definitive treatment.[12] A nationwide prospective study is warranted to gain accurate information on incidence rate, epidemiological distributions, risk factors, treatment outcome and overall survival among AA patients in our country.

ACKNOWLEDGMENT

1. Dr Lily Wong Lee Lee (Consultant Haematologist and Head of Haematology Unit, Department of Medicine, Queen Elizabeth Hospital, Sabah)
2. Dr Chew Lee Ping (Consultant Haematologist and Head of Haematology Unit, Department of Medicine, Sarawak General Hospital, Sarawak)

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper.

REFERENCES

1. Young NS and Kaufmann DW. The epidemiology of acquired aplastic anemia. Haematologica 2008; 93: 489–92.
2. Yong ASM, Goh AS, Rahman M, Menon J, Purushothaman V. Epidemiology of aplastic anaemia in the state of Sabah, Malaysia. Med J Malaysia 1998; 53(1): 59–62.
3. McCahon E, Tang K, Rogers PCJ, McBride ML, Schultz KR. The impact of Asian descent on the incidence of acquired severe aplastic anaemia in children. British Journal of Haematology 2003; 121: 170–2.
4. Vaht K, Goransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, et al. Incidence and outcome of acquired aplastic anemia—real-world data from patients diagnosed in Sweden from 2000–2011. Haematologica 2017; 102(10): 1683–90.

5. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. British Journal of Haematology 2016; 172: 187–207.
6. Department of Statistics Malaysia, Official Portal [Internet]. Putrajaya: Department of Statistics, Malaysia; 2015-2020. Population Distribution and Basic Demographic Characteristic Report 2010; 2011 Aug 5 [cited 2020 May]. Available from: https://www.dosm.gov.my/v1/
7. World directory of minorities and indigenous peoples [Internet]. London: Minority Rights Group International; 2020. Indigenous peoples and ethnic minorities in Sabah; 2018 Jan [cited 2020 May]. Available from: https://minorityrights.org/minorities/indigenous-peoples-and-ethnic-minorities-in-sabah/
8. Dhaliwal JS, Wong L, Kamaluddin MA, Lee YY, Murad S. Susceptibility to aplastic anemia is associated with HLA-DRB1*1501 in an aboriginal population in Sabah, Malaysia. Human Immunology 2011; 72: 889–92.
9. Liu S, Li Q, Zhang Y, Li Q, Ye B, Wu D, et al. Association of Human Leukocyte Antigen DRB1*15 and DRB1*15:01 Polymorphisms with Response to Immunosuppressive Therapy in Patients with Aplastic Anemia: A Meta-Analysis. PLOS ONE 2016; 11(9): e0162382.
10. Li SS, Hsu YT, Chang C, Lee SC, Yen CC, Cheng CN, et al. Incidence and treatment outcome of aplastic anemia in Taiwan—real-world data from single-institute experience and a nationwide population-based database. Annals of Hematology 2019; 98(1): 29–39.
11. Wang W, Wang X, Xu X, Lin G. Diagnosis and Treatment of Acquired Aplastic Anaemia in Adults: 142 Cases from a Multicentre, Prospective Cohort Study in Shanghai, China. The Journal of International Medical Research 2011; 39: 1994–2005.
12. Valdez JM, Scheinberg P, Nunez O, Wu CO, Young NS, Walsh TJ. Decreased infection-related mortality and improved survival in severe aplastic anemia in the past two decades. Clin Infect Dis 2011; 52(6): 726–35.
13. Bacigalupo A. How I treat acquired aplastic anemia. Blood 2017; 129(11): 1428–36.
14. Dufour C, Svahn J, Bacigalupo A. Front-line immunosuppressive treatment of acquired aplastic anemia. Bone Marrow Transplantation 2012; 48: 174–7.

Factors associated with the incidence of low birth weight in Pontianak City, Indonesia

Lidia Hastuti, DHSc[1], Anggi Litasari, MSN[2], Tutur Kardiatun, MSN[1], Ridha Mardiyani, MSN[1], Annisa Rahmawati, MSN[2], Suriadi Jais, PhD[1,3]

[1]Institut Teknologi dan Kesehatan Muhammadiyah Kalimantan Barat, Indonesia, [2]Department of Internist at University Tanjungpura Hospital, Indonesia, [3]Faculty of Medicine, School of Nursing, Tanjungpura University, Indonesia

ABSTRACT

Introduction: The weight of an infant at the time of birth is an indicator of its health. Infants with low birth weight (LBW) are at a higher risk of neonatal mortality and morbidity as well as stunted growth. Low birth weight (LBW) remains a public health concern in developing countries, such as Indonesia. In fact, the neonatal mortalities and morbidities that occur as a consequence of LBW can be prevented by addressing the relevant risk factors. It is believed that by identifying these risk factors, prevention and management efforts can be efficiently and effectively implemented to reduce incidences of LBW (LBWIs). As such, the present study determined the factors affecting LBWIs in a rural setting in Pontianak City, Indonesia.

Materials and methods: This is a retrospective unmatched case-control study. The required data was obtained from the medical records maintained by the University Tanjungpura Hospital, Pontianak City, Indonesia. Simple random sampling was used to select and equally divide the 60 chosen respondents into LBW case and normal birth weight control groups.

Results: Mothers with low educational levels had a 1.5 times greater chance of giving birth to LBW babies. The results of the multivariate analysis also revealed a correlation between gestational age (GA), incidence of premature rupture of membranes (PROM), and intrauterine growth restriction (IUGR) and that their combined effects that contributed to 56% of LBWIs.

Conclusion: Low maternal education level, low gestational age, IUGR, and premature rupture of membranes contribute to LBW babies. This study recommends that it is necessary to educate women of childbearing age about routine antenatal care checks to identify risk factors that can lead to LBW.

KEYWORDS:
Intrauterine growth restriction, Low birth weight, Premature, Risk factors

INTRODUCTION

In 2020, 19.8 million newborns or approximately 14.7% of all babies born globally had low birth weight (LBW). The incidence of LBW in developing countries is 16.5%, which is twice as high as that in developed countries.[1–4] Indonesia is a developing country ranked third among countries with the highest prevalence of LBW (11.1%), after India (27.6%) and South Africa (13.2%). Additionally, Indonesia has the second highest prevalence of LBW among Asian countries, which is at 6.37%[5] after the Philippines (21.2%).[6]

Low birth weight remains a public health concern in developing countries. Babies with LBW are at increased risk of morbidity, stunted growth, and neonatal death.[7] Jaundice has the highest morbidity rate (40.09%) in LBW babies, followed by respiratory problems (18.16%), sepsis (8.72%), and apnoea (4.48%). Premature infants with LBW have the highest morbidity rates from conditions, such as apnoea (100%), birth asphyxia (88.88%), respiratory problems (87.01%), sepsis (80.55%), and jaundice (67.64%). The incidence of LBW is associated with infant mortality,[8] and early neonatal mortality rate is 21.22 per 1000 live births. Low birth weight can lead to death from feed aspiration, sepsis, and hyaline membrane disease.[3]

The proportion of babies with birth weight <2500 g (LBW) from all provinces in Indonesia was 6.2% (this percentage is the average of all LBW cases that occurred throughout Indonesia).[9] Sixteen provinces, namely South Sumatra, Bangka Belitung, West Java, DI Yogyakarta, Banten, West Nusa Tenggara, East Nusa Tenggara, West Kalimantan, Central Kalimantan, Kalimantan, Central Sulawesi, South Sulawesi, South Maluku, North Maluku, West Papua, and Papua, have LBW prevalence rates above the national rate.[10–12]

In the last two years, there has been an increase in the number of cases at Tanjung Pura University Hospital, Pontianak (from 48 to 58 cases). A previous study reported that the factors causing LBW include maternal, baby, and other factors.[13] Another study found that missing iron and folate supplementation during pregnancy, maternal meal frequency during pregnancy, maternal haemoglobin level, food insecurity, and women's inadequate minimum dietary diversity score were significant determinants of LBW.[14] Maternal age, parity, arm circumference, haemoglobin grade, gestational age, and complications during pregnancy were significant maternal risk factors for LBW.[15]

LBW leads to a variety of complications, particularly in developing countries and the Third World. LBW infants who

This article was accepted: 06 November 2024
Corresponding Author: Suriadi Jais
Email: suriadif@yahoo.com.au

survive will face cognitive and neurological disorders, increased risk of high blood pressure, obstructive pulmonary disease, high blood cholesterol, kidney disease, acute watery diarrhea, and immune system disorders.[3,5] LBW also contributes to the development of neurodevelopmental disorders, such as mental retardation and learning disability, as well as psychodevelopmental disorders and chronic diseases in adulthood.[7] Therefore, identifying factors that influence the incidence of LBW is very important. By analyzing risk factors, pregnant women or women of childbearing age will be more alert to prevent LBW births.

Various efforts have been made to prevent LBW, one of which is to optimize antenatal care visits. Antenatal care visits can detect risk factors in pregnant women and enable immediate management; however, implementation is not yet optimal. By identifying the risk factors for LBW, prevention and management efforts can be carried out efficiently and effectively to reduce the incidence of LBW. Several mortalities and morbidities can be prevented by addressing the factors associated with LBW. This study aimed to identify the risk factors associated with LBW.[6]

MATERIALS AND METHODS

The present quantitative study was conducted using a 1:1 comparison unmatched case-control design. Observational analytical epidemiological study examines the relationship between a particular outcome (disease or health condition) and its risk factors. This study included patients with LBW and a control group whose effects were unknown (normal birth weight). Secondary data were obtained from our hospital medical records for the last one year, with a sample size of 60 respondents, comprising 30 cases and 30 controls. Simple random sampling was to select the 60 respondents while taking into consideration the study's inclusion criteria; namely mothers who had given birth in the last one year, mothers who did not have diabetes mellitus and/or hypertension, and mothers living in Pontianak City. Meanwhile, the exclusion criteria included the mothers of babies born gemelli and/or prematurely. The questionnaire was developed by the researchers and comprised three parts that collected the respondent's demographic data, information about the mother's health, and information about the baby's health. Its validity and reliability were tested and deemed valid and reliable.

This study passed the ethical test (ethical permission No. 187/II.1. AU/KET.ETIK/VI/2021). Statistical data analysis was performed using data software, bivariate analysis was performed using the chi-square test, and multivariate analysis was performed using logistic regression analysis.

RESULTS

The present quantitative study was conducted using a 1:1 comparison unmatched case-control design. Observational analytical epidemiological study examines the relationship between a particular outcome (disease or health condition) and its risk factors. This study included patients with LBW and a control group whose effects were unknown (normal birth weight). Secondary data were obtained from our hospital medical records for the last one year, with a sample size of 60 respondents, comprising 30 cases and 30 controls. Simple random sampling was to select the 60 respondents while taking into consideration the study's inclusion criteria; namely mothers who had given birth in the last one year, mothers who did not have diabetes mellitus and/or hypertension, and mothers living in Pontianak City. Meanwhile, the exclusion criteria included the mothers of babies born gemelli and/or prematurely. The questionnaire was developed by the researchers and comprised three parts that collected the respondent's demographic data, information about the mother's health, and information about the baby's health. Its validity and reliability were tested and deemed valid and reliable.

The univariate analysis was used to explain or describe the characteristics of each study variable. The results of statistical tests on characteristics of the respondents based on education, parity, gestational spacing, gestational age, premature rupture of membranes (PROM), pre-eclampsia, antepartum bleeding, intrauterine growth restriction (IUGR), and maternal age in both groups are shown in Table I. The results of the statistical tests showed the characteristics of the respondents in both groups. In the case group, 52.1% of the respondents had low education, while it was 47.9% in the control group. Regarding parity, the percentage of respondents at risk of LBW was 51.3% in the case group and 48.7% in the control group. The results of the statistical tests on pregnancy spacing showed that 55.2% of the respondents in the case group were at risk of LBW, whereas in the control group, it was 44.8%. In the case group, the percentage of respondents with preterm gestational age was 82.4%, whereas it was 17.6% in the control group. The proportion of respondents who experienced PROM in the case group was 81.8%, while it was 18.2% in the control group. The percentage of respondents who experienced pre-eclampsia in the case group was 62.5%, while it was 37.5% in the control group. The percentage of respondents who experienced bleeding in the case group was 60%, while it was 40% in the control group. The percentage of respondents who experienced IUGR in the case group was 87.5%, while it was 12.5% in the control group. For the maternal age, in the case group, 75% of the respondents gave birth in the risk age, while it was 25% in the control group.

In the bivariate analysis, data on the incidence of LBW in both groups were analysed using the chi-square test. The results of the bivariate analysis are presented in Table II. The results of the statistical test showed that there was no significant relationship between mother's educational level and the incidence of LBW ($p = 0.52$; $p>0.05$). Estimation test for low educational level reported an odds ratio (OR) of 1.52 (OR >1, 95% confidence interval (CI): 0.42–5.47), which indicates that respondents who have low education are 1.52 times more likely to have LBW births than those with higher education. For parity, the statistical test reported a p-value of 0.78 ($p>0.05$), indicating that there was no significant relationship between parity and the incidence of LBW. The estimation test reported an OR of 0.86 (OR <1, 95% CI: 0.29–2.49), indicating that parity in the risk category is a protective factor for the incidence of LBW. The results of the statistical tests on pregnancy spacing showed a p-value of 0.44 ($p>0.05$), indicating that there is no significant relationship between pregnancy spacing and the incidence of LBW. The

Table I: The characteristics of respondents in the case and control groups

Characteristics of respondents	Birth weight (n=60)			
	Case (LBW)		Control (NBW)	
	f	%	f	%
Education				
Low education	25	52.1%	23	47.9%
Higher education	5	41.7%	7	58.3%
Parity				
At risk	20	51.3%	19	48.7%
No risk	10	47.6%	11	52.4%
Spacing of pregnancy				
At risk	16	55.2%	13	44.8%
No risk	14	45.2%	17	54.8%
Gestational Age				
Preterm	14	82.4%	3	17.6%
Term	16	37.2%	27	62.8%
PROM				
Yes	9	81.8%	2	18.2%
No	21	42.9%	28	57.1%
Disease				
Pre-eclampsia	10	62.5%	6	37.5%
No pre-eclampsia	20	45.5%	24	54.5%
Bleeding				
Yes	6	60.0%	4	40.0%
No	24	48.0%	26	52.0%
IUGR				
Yes	21	87.5%	3	12.5%
No	9	25.0%	27	75, 0%
Mother's Age				
At risk	3	75.0%	1	25.0%
No risk	27	48.2	29	51.8%

LBW, low birth weight; NBW, normal birth weight; PROM, premature rupture of membranes; IUGR, intrauterine growth restriction

Table II: An analysis of the factors affecting birth weight

Variable	Birth weight (n=60)				X	p	OR	95% CI
	Case (LBW)		Control (NBW)					
	f	%	f	%				
Education								
Low education	25	83.8	23	76.7	0.42	0.52	1.52	0.42–5.47
Higher education	5	16.7	7	23.3			1	
Parity								
At-risk	19	63.3	20	66.7	0.07	0.78	0.86	0.29–2.49
No risk	11	36.7	10	33.3			1	
Spacing of pregnancy								
At-risk	16	53.3	13	43.3	0.60	0.44	1.49	0.54–4.13
No risk	14	46.7	17	56.7			1	
Gestational Age								
Preterm	14	46.7	3	10.0	9.93	0.002*	7.87	1.95–31.67
Term	16	53.3	2	90.0			1	
PROM								
Yes	9	30.0	2	6.7	5.46	0.02*	6.00	1.17–30.72
No	21	70.0	28	81.7			1	
Disease								
Pre-eclampsia	10	33.3	6	20.0	1.36	0.24	2.00	0.62–6.46
No pre-eclampsia	20	66.7	24	80.0			1	
Bleeding								
Yes	6	20.0	4	13.3	0.48	0.48	1.63	0.41–6.47
No	24	80.0	26	86.7			1	
IUGR								
Yes	21	87.5	3	10	22.5	0.000**	21	5.05–87.38
No	9	25.0	27	90			1	
Mother's Age								
At-risk	3	10	1	3.3	1.07	0.31	3.22	0.32–32.89
No risk	27	90	29	96.7			1	

Significant * p<0.05 ** p<0.001
OR, odds ration; CI, confidence interval; LBW, low birth weight; NBW, normal birth weight; PROM, premature rupture of membranes; IUGR, intrauterine growth restriction

Table III.: Multivariate logistic regression analysis

Variable	p	OR (95% CI)
IUGR		
Yes	0.000**	22.07 (4.68–104.08)**
No		1
Gestational Age		
Preterm	0.034*	6.57 (1.15–37.45)*
Term		1
Premature rupture of membranes		
Yes	0.441	2.44 (0.25–23.58)
No		1
-2 log-likelihood		50.87
R2		0.56
Df		3

Significant * p<0.05 p<0.001
OR, odds ration; CI, confidence interval; IUGR, intrauterine growth restriction

estimation test reported an OR of 1.49 (OR >1, 95% CI: 0.54–4.13), indicating that respondents with pregnancy spacing in the risk category have a 1.49 times chance of having LBW compared to those with a spacing not in the risk category. The statistical test for gestational age showed a p-value of 0.002 (p<0.05), indicating a significant relationship between gestational age and the incidence of LBW. The estimation test reported an OR of 7.87 (OR >1, 95% CI: 1.95–31.67), indicating that respondents with preterm gestational age have a 7.87 times chance of having LBW compared to those with term pregnancy intervals. The results of this study also found that there was a significant relationship between PROM and the incidence of LBW, and the statistical test obtained showed a p-value of 0.02 (p<0.05). The estimation test reported an OR of 6 (OR >1, 95% CI: 11.17–30.72), indicating that respondents who experience PROM are six times more likely to have LBW compared to those who do not experience PROM. The statistical test on the incidence of pre-eclampsia showed a p-value of 0.24 (p>0.05), indicating that there is no significant relationship between pre-eclampsia and the incidence of LBW. The estimation test for pre-eclampsia reported an OR of 2 (OR >1, 95% CI: 0.62–6.46), indicating that respondents with pre-eclampsia have a two times chance of having LBW compared to those without pre-eclampsia. The statistical test for bleeding during delivery showed a p-value of 0.31 (p> 0.05), indicating that there is no significant relationship between bleeding and the incidence of LBW. The estimation test reported an OR of 1.63 (OR >1, 95% CI: 0.41–6.47), indicating that respondents who experience bleeding have a 1.63 times chance of having LBW compared to those who do not experience bleeding during childbirth. The chi-square test for IUGR showed a p-value of 0.000 (p<0.05), indicating a significant relationship between IUGR and the incidence of LBW. The estimation test reported an OR of 21 (OR >1, 95% CI: 5.05–87.38), indicating that infants who have IUGR have a 21 times chance of having LBW compared to those who do not have IUGR. The statistical test for maternal age showed a p-value of 0.48 (p> 0.05), indicating that there is no significant relationship between maternal age and the incidence of LBW. The estimation test showed an OR of 3.22 (OR >1, 95% CI: 0.32–32.89), indicating that maternal age in the risk category has a 3.22 times chance of resulting in LBW compared to those whose ages were not in the risk category.

The multivariate analysis was conducted to analyse several factors related to the incidence of LBW. The analysis was carried out at a modelling stage, which aimed to determine the relationship between the independent and dependent variables by considering maternal and foetal factors with the incidence of LBW. The test used was a logistic regression test with a 95% CI, significance at a p-value of <0.05, value of the OR, value of -2 log-likelihood, and R^2. TThe results of the statistical analysis in Table III show the relationship between the independent variables, including maternal and foetal factors (gestational age, incidence of PROM, and IUGR), and dependent variable (incidence of LBW), which were analysed simultaneously. Statistical significance was obtained by calculating the difference in -2 log-likelihood. When the three variables were analysed simultaneously, there was a 0.89 increased risk of LBW incidence for gestational age, 0.25 for PROM, and 1.07 for IUGR. The presence of these three variables simultaneously contributed to a LBW incidence of 56%.

DISCUSSION

The education level of a mother influences behaviour, including meeting nutritional needs through diet and understanding prenatal care during pregnancy. A person's educational background is an important element that can influence their nutritional status and what good things need to be done during pregnancy. With a higher level of education, it is expected that knowledge or information about pregnancy and how to maintain pregnancy until delivery can be obtained. Thus, baby care is expected to improve. This study found that although maternal education was not statistically significant in the incidence of LBW, the estimation test showed that mothers with low educational levels had a 1.5 times greater chance of giving birth to LBW babies than those with higher education. This statement is supported by a previous study, which reported that low educational level affects a baby's birth weight; mothers with low educational level tend to give birth to babies with LBW. However, educational level was not a risk factor for LBW. This is because a mothers' knowledge is not just a race for final academic education. However, there is an advancement among younger mothers in accessing and obtaining information, as well as the role of the midwives in providing information, education, and communication to pregnant

women during antenatal visits. These results are consistent with the results of this study because the frequency and antenatal care quality of majority of the respondents were good.[16,17]

Parity is an important factor affecting foetal health during pregnancy. A high-parity state increases the risk of LBW because the ability of the uterus to provide nutrients during pregnancy is reduced, thereby hampering the distribution of nutrients between the mother and foetus. The results of previous studies reported that at parity >3, the risk was 0.92 times higher than that at parity ≤3.18 Too many deliveries in the mother can result in a decrease in the function of the mother's reproductive system.[17] Low birth weight can occur with parity as a risk factor because the mother's reproductive system has experienced thinning due to frequent childbirth; this is due to the high parity of the mother and decrease in endometrial quality. This study is in line with a previous study that found that respondents with parity in the risk category are 0.86 times likely to give birth to LBW babies.[18] The first or more than three deliveries can harm the mother and foetus. After three deliveries, the mother is at risk of giving birth to a baby with disabilities or LBW. More than three child birth increase the health risk of pregnancy and maternity mothers, which can cause complications for both mother and baby, resulting in LBW babies. This study is also in line with previous studies that showed no significant relationship between parity and the incidence of LBW ($p>0.05$).[19]

In healthy reproduction, the safe age for pregnancy and childbirth is 20–35 years, whereas those at risk for pregnancy and childbirth are those aged <20 years or >35 years.[20] The results of this study are in line with the results of previous study, which showed that there was no significant relationship between maternal age and the incidence of LBW ($p>0.05$).[19] Meanwhile, the results of other studies reported that there was a relationship between maternal age and the incidence of LBW, namely the age of the mother at risk with p-value = 0.014 ($p<0.05$).6 The difference is that based on the results of a previous study, it is thought that only a small number of maternal factors were studied, whereas there are many factors that can influence the incidence of LBW, including foetal, placental, and environmental factors. Other risk factors that influence LBW births are external factors, including the mother's work activities and economic status, and internal factors, such as the mother's age, pregnancy spacing, parity, pregnancy checks, maternal nutritional status, pregnancy history, and pregnancy complications.[21]

Pregnancies that are too close together prevent the reproductive organs from functioning optimally, resulting in poor foetal growth. Additionally, infants can experience LBW, poor nutrition, and shorter breastfeeding times. A good pregnancy interval for the health of a mother and child is >2–5 years; the shorter (<2 years) the pregnancy interval, the higher the risk of developing pre-eclampsia and other pregnancy complications, which have severe effects on the baby, such as early delivery or small for gestational age, thereby leading to LBW.[18] The ideal gestational interval between births is >2 years, which allows the body to repair and prepare the reproductive organs for the next pregnancy. A disturbed reproductive system hinders foetal development and growth, and a pregnancy interval of <2 years can pose foetal risks, one of which is LBW.[19] The results of this study are in line with those of previous studies, which reported no significant relationship between pregnancy interval and the incidence of LBW ($p>0.05$).[18] However, other studies found a relationship between birth spacing and the incidence of LBW.[23] Differences in results and studies can be explained because they are not always caused by birth spacing. Other risk factors that influence LBW are external factors, including the mother's work activities and economic status, and internal factors, including the mother's age, pregnancy spacing, parity, pregnancy checks, maternal nutritional status, pregnancy history, and pregnancy complications.[4,5,24]

Gestational age groups are divided into preterm (<37 weeks), term (37–42 weeks), and post-term (42 weeks). A baby's weight increases according to gestational age because the shorter the pregnancy period, the less perfect the growth of the body's organs, which affects the baby's birth weight. The risk factor of gestational age is related to the incidence of LBW; a gestational age of <37 weeks can be one of the factors causing LBW because foetal growth is not yet complete at this age; this affects the baby's birth weight. This study is in line with previous findings that showed a relationship between gestational age and the incidence of LBW, and that mothers who experience premature pregnancy have 15-fold risk of experiencing LBW compared to those with full-term gestation.[25]

Pre-eclampsia is a potentially dangerous pregnancy complication characterized by high blood pressure. It usually begins after 20 weeks of gestation or after delivery and is characterized by an increase in blood pressure of up to 140/90 mmHg, accompanied by increased levels of proteinuria. One of the maternal diseases that can affect a baby's weight at birth is pre-eclampsia, which can cause IUGR, resulting in a smaller and weaker baby at birth. This condition allows babies to be born with LBW. Other studies have shown that mothers who experience pre-eclampsia are twice as likely to give birth with LBW infants than those who do not experience pre-eclampsia, although the relationship between the two is not statistically significant. The results of this study are in line with previous studies that found no relationship between pre-eclampsia and the incidence of LBW.[26]

Bleeding during pregnancy is the leading cause of maternal and perinatal death, although the specific cause is unknown. In late pregnancy, considerable vaginal bleeding can occur due to detachment of the placenta from the uterine wall (placenta abruption) and tear in the implantation site of the placenta that partially covers the birth canal (placenta previa), which can cause LBW. Previous studies have reported that antepartum bleeding affects LBW. The difference with previous studies can be due to other factors that affect LBW; antepartum bleeding can affect foetal growth and cause LBW. Mechanical trauma and severity of bleeding are also thought to influence the incidence of LBW. In this study, no further investigation of bleeding or causes of bleeding was conducted. Further studies using primary data and other methods are necessary.

Premature rupture of membranes refers to premature rupture of the amniotic fluid. If the membranes rupture before 37 weeks of pregnancy, it is called premature rupture of the membranes. Premature rupture of membranes also affects the incidence of LBWs. Premature rupture of membranes can be caused by infection. This infection can result from the biomechanical process of amniotic fluid in the form of protein hydrolysate; this is because the strength of the amniotic fluid is weak, and connective tissue and blood vessels are lacking, which can cause premature birth. This study is in line with previous studies that explained that one of the factors associated with the incidence of LBW is PROM.[27]

Based on the researchers' conclusions, there is a relationship between IUGR factors and the incidence of LBW. Low birth weight can also occur at 37–42 weeks of gestation, and may be caused by foetal growth disorders (IUGR) due to malnutrition before and during pregnancy, which play a major role. The foetus in the uterus grows and develops as its mother ages. Most foetuses have a small size and weight when they are born too early (premature birth). However, babies can also have a small size and weight, even if they are born at term. This condition is known as IUGR. The two main causes of LBW are premature birth and slow foetal growth (IUGR). Mothers with anaemia during pregnancy or those with IUGR can give birth to small babies. A mother's need for nutrients increases in multiple pregnancies, which causes anaemia and other deficiency diseases, resulting in delivery of small babies.[28] During pregnancy, mothers require additional calories, proteins, and minerals for the growth of the foetus, placenta, and uterine tissue. Generally, the pregnancy of a premature baby with LBW is related to a situation in which the uterus is unable to maintain the foetus, disturbances during pregnancy, or stimulation that causes uterine contractions before maturity.

The limitations of the present study include a small sample size and respondent characteristics that did not match between the two groups. Therefore, more studies should be conducted with a larger sample size and respondent characteristics that match between the two groups. The findings of the present study may prevent unnecessary risks as well as improve maternal and infant health. It is believed that, by identifying the factors influencing LBWIs, it may be prevented from occurring. This would not only affect the short-term health of the infant, but its health in the long run as well. Lastly, the findings of the present study may be used to develop maternal and child health programmes that effectively decrease the new-born mortality rate.

CONCLUSION

This study found that gestational age, IUGR, and premature rupture of membranes were associated with the incidence of LBW. The presence of these three variables simultaneously contributed to an LBW incidence of 56%. This study recommends that it is necessary to educate women of childbearing age about routine antenatal care checks to avoid risk factors that can cause LBW. Further studies can be performed with a larger sample size and examine the socio-cultural aspects that affect the incidence of LBW.

ACKNOWLEDGEMENT

We thank the P3MI ITEKES Muhammadiyah Kalimantan Barat Centre for facilitating research activities, Management of the Tanjung Pura University Hospital Pontianak, and all the study respondents.

CONFLICT OF INTEREST

Authors declared no conflicts of interest.

REFERENCES

1. Herawati S, Tridiyawati F. Risk Factor Analysis Of Low Birth Weight Events (LBW) At Kartika Husada Hospital. Int J Heal Pharm 2023;3(4): 646–51.
2. Mehare T, Sharew Y. Prevalence and Associated Factors of Low Birth Weight among Term Newborns in Dilla Town, Southern Ethiopia. Int J Pediatr (United Kingdom) 2020; 2020: 1–7.
3. Pabbati J, Subramanian P, Renikuntla M. Morbidity and mortality of low birth weight babies in early neonatal period in a rural area teaching hospital, Telangana, India. Int J Contemp Pediatr 2019; 6(4): 1582.
4. Amelia L. Posisi Nesting Terhadap Periode Tidur-Bangun Bayi Prematur Di Rumah Sakit Umum Daerah Dr . Soedarso Pontianak. J Keperawatan dan Kesehat 2018; 9(1): 9–16.
5. Pramono MS, Paramita A. Pola Kejadian Dan Determinan bayi Dengan Berat Badan Lahir Rendah (Bblr) Di Indonesia Tahun 2013 (Pattern of Occurrence and Determinants of Baby with Low Birth Weight in Indonesia 2013). Bul Penelit Sist Kesehat 2015; 18(1): 1-10.
6. Anil KC, Basel PL, Singh S. Low birth weight and its associated risk factors: Health facility-based case-control study. PLoS One 2020; 15(6): 1–10.
7. Arsyi M. Maternal Factors Affecting the Incidence of Low Birth Weight (LBW) in Indonesia. Int J Pharm Res 2021; 13(1): 4197-203.
8. Jana A, Saha UR, Reshmi RS, Muhammad T. Relationship between low birth weight and infant mortality: evidence from National Family Health Survey 2019-21, India. Arch Public Heal 2023; 81(1): 1–14.
9. Ramadhaniyati R. Gambaran Pengetahuan Perawat Dalam Pelaksanaan Perawatan Metode Kanguru (PMK) Pada Bayi Berat Lahir Rendah (BBLR) Di Ruang Perinatologi Rsud Sultan Syarif M. Al Qadrie Kota Pontianak. J Keperawatan dan Kesehat 2015; 6(3): 111–6.
10. Wahyuni S, Putri ARA, Imbir S. The Relationship Of Anemia In Pregnancy With The Event Of LBW Babies (Low Birth Weight) at Supiori Hospital. J Kebidanan Kestra 2022; 4(2): 108–12.
11. Erani Asri, Dary, Rifa Tampubolon. Gambaran Perawatan pada Bayi dengan Berat Badan Lahir Rendah. J Keperawatan dan Kesehat 2023; 14(1): 79–88.
12. Lukita Y. Hubungan Status Gizi Ibu Dengan Bayi Berat Badan Lahir Rendah Di Rumah Sakit Soedarso Pontianak. J Keperawatan dan Kesehat 2016; 6(3): 146–9.
13. Dewie S, Shinta S. Analisis faktor-faktor yang mempengaruhi kejadian bblr di puskesmas perkotaan kabupaten banjarnegara. Politek Banjarnegara 2012; 1–6: 1–6.
14. Seid L, Lakhdari D, Berkani M, Belgherbi O, Chouder D, Vasseghian Y, et al. High-efficiency electrochemical degradation of phenol in aqueous solutions using Ni-PPy and Cu-PPy composite materials. J Hazard Mater 2022; 423(PA): 126986.
15. Lestari JF, Etika R, Lestari P. Maternal Risk Factors of Low Birth Weight (Lbw): Systematic Review. Indones Midwifery Heal Sci J 2021; 4(1): 73–81.
16. Sholiha H, Sumarmi S, Studi PS, Masyarakat K, Gizi Kesehatan D. Analisis Risiko Kejadian Berat Bayi Lahir Rendah (Bblr) Pada Primigravida. Media Gizi Indones 2015; 10(1): 57–63.

17. Monita F, Suhaimi D, Ernalia Y. Hubungan Usia, Jarak Kelahiran Dan Kadar Hemoglobin Ibu Hamil Dengan Kejadian Berat Bayi Lahir Rendah. J Kesehat Indones 2019; 2(1): 11–7.
18. Indrasari N. Faktor Resiko pada Kejadian Berat Badan Lahir Rendah (BBLR). J Ilm Kesehat Delima 2012; 8(2): 114–22.
19. Febrianti R. Faktor-Faktor Risiko Yang Mempengaruhi Kejadian Berat Badan Lahir Rendah (Bblr) Di Rsup Dr. M. Djamil Padang Tahun 2019. Sci J 2019; 8(1): 464–9.
20. Apriani E, Ahmad S, Khusni M ahmad. Tens : Hubungan Usia Ibu Hamil , Paritas dan Usia Kehamilan. Trends Of Nursing Sci 2021; 1(3): 45-52.
21. Ekasari WU, Wati DS. Analysis of the factors that influence the incidence of low birth weight at the Purwodadi II health center. Jurnal Profesi Bidan Indonesia 2023; 3(1): 42–50.
22. Padma P, Rawida W gede bagus. Analisis faktor risiko bayi Berat Badan Lahir Rendah (BBLR) di Unit Pelayanan Terpadu (UPT) Kesehatan Masyarakt (Kesmas) Gianyar I tahun 2016-2017. Intisari Sains Media 2019; 10(3): 647–78.
23. Nabila Aswina Putri, Dewi Anggriani Harahap A. The Relationship Between Preeclampsia And The Incidence of Low Birth Weight Babies At The Fatiha Clinic. Evid Midwifery J 2024; 3(1): 2963-413X.
24. Budjana DW, Isnaini N, Hatta M. Analisis Faktor Resiko Stunting. J Keperawatan dan Kesehat 2023; 14(1): 40–50.
25. Liznindya L. Hubungan Usia Ibu Hamil dengan Kejadian Bayi Berat Lahir Rendah (BBLR) Di Desa Serangmekar Ciparay Kab. Bandung Tahun 2021. Cerdika J Ilm Indones 2023; 3(1): 1–5.
26. Inpresari I, Pertiwi WE. Determinan Kejadian Berat Bayi Lahir Rendah. J Kesehat Reproduksi 2021; 7(3): 141.
27. Setiati AR, Rahayu S. Faktor Yang Mempengaruhi Kejadian BBLR (Berat Badan Lahir Rendah) Di Ruang Perawatan Intensif Neonatus RSUD DR Moewardi Di Surakarta. J Keperawatan Glob 2017; 2(1): 9–20.
28. Suhartati S, Rahmawaty L, Mulia SS, Mulia AS. Hubungan Anemia Pada Ibu Hamil Kejadian Berat Badan Lahir Rendah Di Wilayah Kerja Puskesmas Tabalong Tahun 2016. Dinamika Kesehatan 2017; 8(1): 42-51.

ORIGINAL ARTICLE

Effect of transcutaneous electrical acupoint stimulation in heart rate variability in post-on-call trainees

Low Hsueh Jing, MMed (Anaesth)[1], Cheah Onn Kee, MMed (Anaesth)[1], Ng Boon Hau, MMed[2], Siti Nidzwani Mohamad Mahdi, MMed (Anaesth)[1], Wan Rahiza Wan Mat, MMed (Anaesth)[1], Liu Chian Yong, MMed (Anaesth)[1]

[1]Department of Anaesthesia and Critical Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia, [2]Respiratory Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Anaesthesiology is a high-demand speciality with 24-hour on-call shifts, which can lead to significant stress and impaired sleep quality among anaesthetists. Non-pharmacological interventions like acupuncture have been widely explored for stress relief. This study aims to evaluate the impact of transcutaneous electrical acupoint stimulation (TEAS) on physiological parameters, specifically heart rate variability (HRV) and sleep quality, in anaesthesiology trainees following 24-hour on-call duty.

Materials and Methods: A total of 38 anaesthesiology trainees, following 24-hour ICU on-call shifts, were recruited for this single-centre cross-sectional clinical trial. The participants were required to complete two 24-hour on-call duties. Demographic data and baseline sleep quality assessments were collected following the first on-call duty. Upon completion of the second on-call shift, participants underwent 20 minutes of TEAS at bilateral PC6 (Neiguan), LI4 (Hegu), LR3 (Taichong), and ST41 (Jiexi) points. Heart rate variability (HRV) parameters, blood pressure, and heart rate were recorded before and after TEAS. Post-TEAS sleep quality was assessed following an overnight rest.

Results: The results demonstrated a significant reduction in systolic blood pressure compared to baseline (109.5±8.9 vs 111.9±10.1 mmHg, p = 0.006), as well as a significant decrease in diastolic blood pressure (69.3±8.0 vs 70.9±9.0 mmHg, p = 0.037) and heart rate (65.8±9.2 vs 67.4±9.8 bpm, p = 0.034). There was significant improvement in all aspects of sleep quality (p < 0.001). However, no statistically significant changes were observed in heart rate variability (HRV) parameters, including high-frequency (HF) power, low-frequency (LF) power, and the LF/HF ratio.

Conclusion: TEAS may offer potential benefits in managing cardiovascular stress and improving sleep quality in high-stress environments, such as post-call recovery. Nevertheless, its impact on autonomic nervous system regulation, as reflected by HRV, appears limited.

KEYWORDS:
Transcutaneous electrical acupoint stimulation, acupuncture, heart rate variability, sleep quality

INTRODUCTION

Anaesthesiology is a rapidly evolving medical speciality that plays a critical role in peri-operative care, emergency management, intensive care, and pain management. However, it is a high-stress field characterised by long, unpredictable working hours and demanding academic expectations.[1-3] Anaesthetists frequently face extended shifts and on-call duties, leading to substantial on-call stress. Contributing factors include sleep deprivation, patient care uncertainties, time pressure for decision-making, and heavy workloads.[4,5] If not properly managed, these stressors can result in chronic fatigue, burnout, and an increased risk of cardiovascular and metabolic diseases.[6]

Prolonged on-call duties also disrupt sleep patterns, leading to circadian rhythm disturbances and chronic sleep disorders.[7] Insufficient sleep can impair cognitive function, decrease alertness, and negatively affect work performance, heightening the risk of medical errors.[8] Early detection of sleep issues and timely interventions to improve sleep quality are essential to safeguard the health of anaesthetists and ensure the safe delivery of patient care.

Non-pharmacological interventions like acupuncture have been widely explored for stress relief. Acupuncture, rooted in Traditional Chinese Medicine, involves stimulating specific acupoints to restore the balance of Qi, a form of bioenergy.[9,10] Among commonly used acupoints, PC6 (Neiguan) is known for its cardiac protection, while LI4 (Hegu), LR3 (Taichong), and ST41 (Jiexi) are associated with general health and immune function.[11-16] Modern adaptations, such as transcutaneous electrical acupoint stimulation (TEAS), offer needleless alternatives that are easier to standardise, less invasive, and more accessible.[17]

Stress is closely linked to dysregulation of the autonomic nervous system (ANS), which can be assessed through heart rate variability (HRV).[18] HRV analysis, particularly frequency-domain parameters such as low-frequency power (LF), high-frequency power (HF), and the LF/HF ratio, provides insights into sympathovagal balance and ANS function.[19-24] This study aimed to assess the impact of TEAS on HRV and sleep quality in anaesthesiology trainees after 24-hour on-call shifts.

This article was accepted: 10 October 2024
Corresponding Author: Ng Boon Hau
Email: ngboonhau@hotmail.com

MATERIALS AND METHODS

This cross-sectional study, with project code JEP-2021-912, was conducted with approval from the Medical Research and Ethics Committee of Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia.

Anaesthesiology post-graduate trainees who had completed a 24-hour on-call duty in the intensive care unit (ICU) were recruited. Written informed consent was obtained prior to participation. Exclusion criteria included known psychiatric or sleep disorders, cardiac diseases, use of cardiac implantable electronic devices, cigarette or alcohol consumption within 24 hours prior to the on-call duty, and skin infections at acupoint sites.

Participants completed two separate 24-hour ICU on-call duties. After the first duty, they were instructed to rest overnight and completed demographic data and sleep quality assessments the following day (pre-TEAS data). Following the second 24-hour on-call duty, participants attended a TEAS intervention session. Caffeinated beverages were prohibited on the morning of the intervention. The session took place in a quiet, air-conditioned room, where participants wore a Polar H10 heart rate monitor with a chest strap positioned at the xiphoid process. Baseline blood pressure (BP), heart rate (HR), and heart rate variability (HRV) parameters were recorded after a 10-minute rest.

The acupoints PC6 (Neiguan) and LI4 (Hegu) on the upper limbs and LR3 (Taichong) and ST41 (Jiexi) on the lower limbs were identified bilaterally. These areas were cleaned with alcohol swabs, and electrode pads were applied to the acupoints. Ipsilateral electrodes were connected in series—PC6 to LI4 and LR3 to ST41—and a continuous wave stimulation at 5 Hz was delivered using an electroacupuncture machine (Hwato SDZ III) for 20 minutes. TEAS stimulation intensity was gradually increased to each participant's maximum tolerance of tingling or numbness in the hands and legs. After the session, participants rested for 10 minutes, after which post-intervention BP, HR, and HRV parameters were recorded. The following morning, after overnight rest, participants completed post-TEAS sleep quality assessments.

Study Research Tool

Heart Rate Variability Assessment

Autonomic nervous system (ANS) function was assessed using HRV analysis. The following frequency-domain indices were defined and measured: high-frequency power (HF; 0.15–0.4 Hz), low-frequency power (LF; 0.04–0.15 Hz), and the LF/HF ratio, representing the ratio of low-frequency to high-frequency HRV.

Likert Scale for Sleep Quality Feedback

This study employed a self-reported sleep quality feedback tool, utilizing a 10-point Likert scale with endpoints ranging from 'worst quality' (score of 1) to 'best quality' (score of 10). The scale evaluated five aspects of sleep quality: sleep duration (total sleep over 24 hours), sleep efficiency (ease of falling and returning to sleep), overall sleep quality (ability to maintain sleep and the presence of disturbances), satisfaction (subjective perception of sleep), and daytime alertness (ability to remain attentive).

A pilot study was conducted to assess the face validity and reliability of the sleep quality feedback. Five participants not involved in the main study were tested to ensure clarity and comprehension of the feedback items, with all expressing good understanding. A reliability analysis was performed on 155 subjects not involved in the interventional study using Cronbach's alpha. The analysis demonstrated a Cronbach's alpha coefficient of 0.882, indicating excellent internal consistency ($\alpha > 0.70$) across the four main items related to sleep quality.

The study did not incorporate validated sleep quality questionnaires, as their methodology did not align with the specific criteria of these instruments.[25]

Devices

Sensor

The Polar H10 HR sensor chest strap is a commercially available HRV monitor designed to detect cardiac electrical activity. Its reliability has been validated against the gold standard for measuring R-R intervals using an ECG Holter monitor.[26]

Output Display

The heart rate monitor was connected via Bluetooth to a smartphone running the EliteHRV© application. The app analysed the heart's electrical signals, providing frequency-domain data on HRV, including HR, LF power, HF power, and the LF/HF ratio. Cross-validation studies have demonstrated that HRV measurements obtained through this smartphone application are reliable when compared to conventional ECG-derived parameters.[27]

Intervention Device

The electroacupuncture device employed for transcutaneous electrical acupoint stimulation (TEAS) therapy was the Hwato Electronic Acupuncture Treatment Instrument, model SDZ-III. This device delivered continuous wave stimulation at a frequency of 5 Hz for 20 minutes, with an optimal intensity ranging from 6 to 15 mA, adjusted according to the trainees' maximum tolerance to maintain minor muscle twitches.

Acupoints

TEAS electrode pads were applied to the following acupoints:

1. PC6 (Neiguan) is located 4cm proximal to the wrist crease, between the tendons of the extensor carpi radialis and palmaris longus (Figure 1A).
2. LI4 (Hegu) is located on the dorsum of the hand, between the first and second metacarpal bones, at the midpoint of the second metacarpal bone and close to its radial border (Figure 1B).
3. LR3 (Taichong) is located on the dorsum of the foot in the distal hollow at the junction of the first and second metatarsal bones (Figure 1C).
4. ST41 (Jiexi) is located at the midpoint of the transverse crease of the ankle joint, between the tendons of the extensor digitorum longus and hallucis longus (Figure 1D).

Statistical Analysis

The sample size was determined with an alpha value set at 0.05 and a power of 80%. The calculation was based on a previous study by Wu et al., which reported a mean

Table I: Demographic data of participants. Data were presented as mean (standard deviation) or frequency (percentage), as appropriate

Variables	Trainees (n=38)
Age (years)	34.5+1.8
BMI (kg/m^2)	24.1+3.4
Gender	
Male	22(57.9)
Female	16(42.1)
Race	
Chinese	18(47.4)
Malay	11(28.9)
Indian	6(15.8)
Other	3(7.9)

Table II: Heart Rate Variability Parameters of Participants before and after TEAS. Data were presented as median [25th–75th percentile], as appropriate

Parameters	Pre TEAS	Post TEAS	p-value
Low Frequency (LF) (ms^2)	885.6 [545.7-1445.9]	870.2[497.8-2063.0]	0.46
High Frequency (HF) (ms^2)	845.4 [397.1-1469.9]	637.8[427.6-1664.4]	0.83
LF: HF Ratio	1.1[0.6-2.2]	1.0[0.6-2.0]	0.65

*p value < 0.05 (overall comparison) with Wilcoxon Signed Ranks Test

Table III: Blood Pressure and Heart Rate before and after TEAS. Data were expressed in mean ± standard deviation as appropriate

Variables	Pre TEAS	Post TEAS	p-value
SBP (mmHg)	111.9±10.1	109.5±8.9	0.006*
DBP (mmHg)	70.9±9.0	69.3±8.0	0.037*
HR (bpm)	67.4±9.8	65.8±9.2	0.034*

*p value < 0.05 (overall comparison) with paired t-test.

Table IV: Sleep Quality Items Feedback. Data were expressed in median [25th-75th percentile] as appropriate

Parameter	Pre TEAS	Post TEAS	p-value
Sleeping Duration (hours)	7.00[6.00-7.00]	7.00[6.00-8.00]	<0.001
Efficiency	7.00[4.75-8.00]	9.00[8.00-9.25]	<0.001
Quality	7.00[5.00-8.00]	9.00[8.00-9.25]	<0.001
Satisfaction	6.00[4.75-7.25]	9.00[8.00-9.25]	<0.001
Alertness	6.00[4.75-7.00]	9.00[8.00-9.25]	<0.001

*p value < 0.05 (overall comparison) with Wilcoxon Signed Ranks Test.

difference in heart rate variability (HRV) of 5.67 beats per minute and a standard deviation of 11.3 beats per minute. Using the Snedecor and Cochran formula, the required sample size, accounting for a 10% dropout rate, was calculated to be 37.[28]

Data analysis was conducted using SPSS for Windows version 23.0 (IBM Corp, Armonk, NY, USA). Results are presented as mean (standard deviation), median (interquartile range), or frequency (percentage) as appropriate. An independent-sample paired t-test was utilised for comparisons of blood pressure and heart rate. The Wilcoxon signed-rank test was applied for the comparative analysis of HRV parameters (LF, HF, LF/HF ratio) and sleep quality items. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Thirty-eight participants were recruited for the study. Demographic data for these participants are presented in Table I.

As shown in Table II, the frequency domain analysis of HRV, including LF power, HF power, and the LF/HF ratio, did not demonstrate significant differences before and after TEAS treatment.

As seen in Table II, SBP, DBP, and HR showed significant reductions following TEAS compared to measurements taken before TEAS.

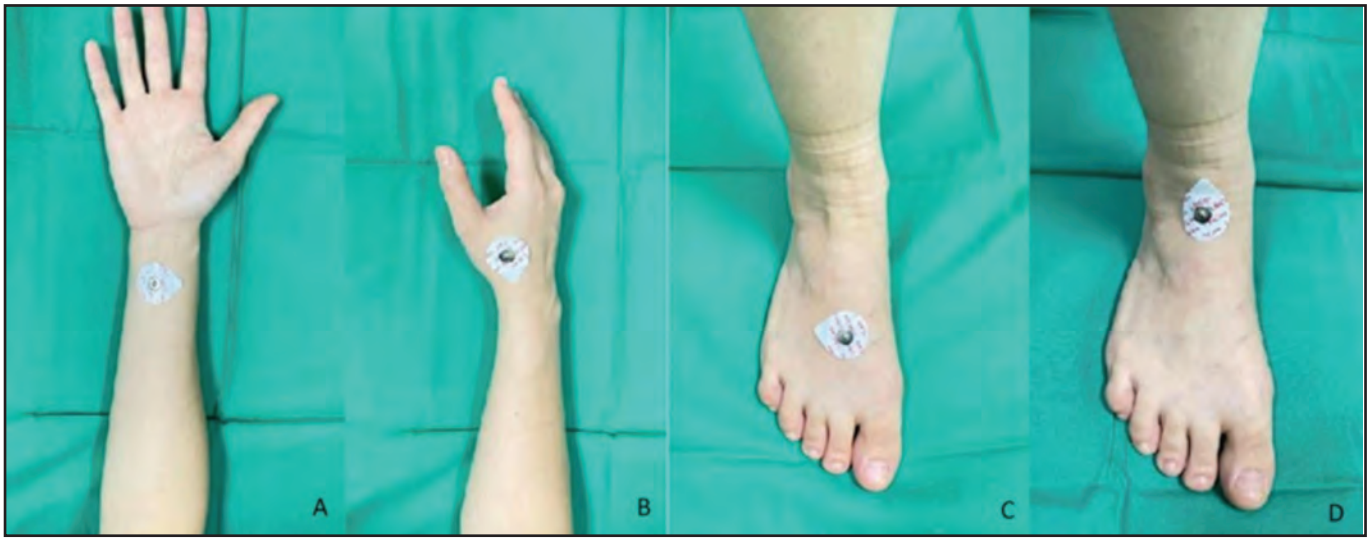

Fig. 1: (A) PC6 Neiguan. (B) LI4 Hegu. (C) LR3 Taichong. (D) ST41 Jiexi

Significant improvement was seen in all five sleep items, including the duration of sleep, sleep efficiency, sleep quality, sleep satisfaction, and alertness. However, a notable disparity was seen in the sleep items after TEAS, with a p-value less than 0.05, as shown in Table IV.

DISCUSSION

Numerous studies have explored various acupuncture techniques for stress reduction. In our study, we found improvements in SBP, DBP, HR, and sleep quality following TEAS. However, we observed no significant changes in HRV parameters. This finding contrasts with Wu et al., who reported that laser acupuncture stimulation at the PC6 (Neiguan) acupoint modulated the ANS by inhibiting sympathetic activity and enhancing vagal tone, leading to improvements in LF, HF, and LF/HF ratio, which in turn reduced stress.[29] In our study, the lack of significant HRV improvement may be attributed to the healthy status of our participants, who exhibited intact ANS functioning capable of effective physiological autoregulation of blood pressure and heart rate.[30] Moreover, our study involved only a single session of TEAS therapy. Sparrow et al. indicated that longer durations of acupuncture treatment over weeks to months may be necessary to observe significant reductions in the LF/HF ratio, reflecting decreased physiological stress.[31]

Our findings indicate a reduction in physiological parameters such as SBP, DBP, and HR post-TEAS intervention among trainees, aligning with studies by Haker et al. and Wei et al., which demonstrated significant reductions in mean HR following LI4 (Hegu) acupoint stimulation in healthy subjects. However, those studies did not observe significant changes in SBP and DBP after therapy.[32] In contrast, Nishijo et al. reported a reduction in heart rate following PC6 (Neiguan) stimulation, while Kimura et al. noted significant decreases in SBP and HR in patients with mild hypertension after acupuncture at multiple acupoints, including PC6, LI4, LR3, ST41, and GV20.[33] Although our results were statistically significant, the observed reductions in physiological parameters were minimal and may lack clinical significance.

Our study showed a significant improvement in sleep satisfaction from baseline after the TEAS session compared to sleep satisfaction without TEAS therapy. Lee et al. reported that acupuncture at HT7 (Shenmen) and PC6 (Neiguan) served as an effective therapeutic approach for insomnia post-stroke by reducing sympathetic hyperactivity.34 Similarly, Chiou et al. found that TEAS effectively enhanced pain, mood, and sleep quality in patients with spinal cord injuries and myofascial pain when applied for seven consecutive days at LI4 and PC7 acupoints.[35] Furthermore, Song et al. demonstrated improved postoperative sleep efficiency in their subjects after TEAS.[36] The mechanism behind these effects may involve neuroendocrine modulation through the regulation of neurotransmitters and endogenous substances, thereby influencing sleep quality.[37] TEAS has been associated with increased levels of serotonin, oxytocin, acetylcholine, and gamma-aminobutyric acid (GABA), alongside decreased levels of glutamate, norepinephrine, and dopamine, all of which contribute to improved sleep quality. Additionally, elevated melatonin levels facilitate sleep-wake regulation, while endogenous substances such as enkephalins, endomorphins, and beta-endorphins possess anxiolytic and mood-modulating properties that enhance sleep health.[37] Another plausible explanation is that TEAS may stabilize cerebral electrical activity by activating hippocampal δ waves and inhibiting β waves, thus reducing neuronal stress and exerting sedative and hypnotic effects that promote better sleep quality.[38]

LIMITATIONS

This study exclusively evaluates the effects of a single-session TEAS intervention on HRV. We lack data on the effects of longer durations or multiple sessions of TEAS treatment. The acupoint selection was based on a generalized formula and may not have been individualized for all participants. Traditional Chinese Medicine emphasises personalised

treatment through syndrome differentiation, suggesting that a standardised acupoint approach may not yield optimal effects. Lastly, while the on-call hours were standardized, variations in workload among different shifts could still influence outcomes.

CONCLUSION

A single session of TEAS was found to significantly reduce systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) while also markedly improving sleep quality in anaesthesiology trainees following 24-hour ICU on-call duty. Despite these positive outcomes, TEAS did not produce any significant changes in heart rate variability (HRV) parameters. These findings suggest that TEAS may offer potential benefits in managing cardiovascular stress and improving sleep quality in high-stress environments, such as post-call recovery. Still, its impact on autonomic nervous system regulation, as reflected by HRV, appears limited.

CONFLICT OF INTEREST

None

FUNDING

None

REFERENCES

1. Bakshi SG, Divatia JV, Kannan S, Myatra SN. Work-related stress: A survey of Indian anesthesiologists. J Anaesthesiol Clin Pharmacol 2017; 33(1): 86-91.
2. Nyssen, A.-S. and I. Hansez. Stress and burnout in anaesthesia. Curr Opin Anesthesiol 2008;21(3): 406-11.
3. van der Wal, R.A.B., J. Wallage, and M.J.L. Bucx. Occupational stress, burnout and personality in anesthesiologists. Curr Opin Anaesthesiol 2018; 31(3): 351-6.
4. Lindfors PM, Nurmi KE, Meretoja OA, Luukkonen RA, Viljanen AM, Leino TJ, et al. On-call stress among Finnish anaesthetists. Anaesthesia 2006;61(9): 856-66.
5. Sanfilippo F, Noto A, Foresta G, Santonocito C, Palumbo GJ, Arcadipane A, et al. Incidence and Factors Associated with Burnout in Anesthesiology: A Systematic Review. BioMed Research International 2017:8648925.
6. Moreno CRC, Marqueze EC, Sargent C, Wright Jr KP, Ferguson SA, Tucker P, et al. Working Time Society consensus statements: Evidence-based effects of shift work on physical and mental health. Industrial Health 2019; 57(2): 139-57.
7. Walker WH 2nd, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. Transl Psychiatry 2020; 10(1): 28.
8. Wali SO, Qutah K, Abushanab L, Basamh R, Abushanab J, Krayem A. Effect of on-call-related sleep deprivation on physicians' mood and alertness. Ann Thorac Med 2013; 8(1): 22-7.
9. Vickers A, C Zollman. ABC of complementary medicine. Acupuncture. BMJ 1999; 319(7215): 973-6.
10. White A, E Ernst. A brief history of acupuncture. Rheumatology (Oxford), 2004. 43(5): 662-3.
11. WH Liu, C Chen, F Wang, SN Guo, Y Hao, SD Li. Development trend and current situation of acupuncture-moxibustion indications. World Journal of Acupuncture - Moxibustion, 2020; 30(4): 245-50.
12. Li H, Wu C, Yan C, Zhao S, Yang S, Liu P, et al. Cardioprotective effect of transcutaneous electrical acupuncture point stimulation on perioperative elderly patients with coronary heart disease: a prospective, randomized, controlled clinical trial. Clinical Interventions in Aging 2019; 14: 1607-14.
13. Lu SF, Huang Y, Wang N, Shen WX, Fu SP, Li Q, et al. Cardioprotective Effect of Electroacupuncture Pretreatment on Myocardial Ischemia/Reperfusion Injury via Antiapoptotic Signaling. eCAM 2016: 1-9.
14. Shan Y, Wang ZQ, Zhao ZL, Zhang M, Hao SL, Xu JY, et al. An fMRI Study of Neuronal Specificity in Acupuncture: The Multiacupoint Siguan and Its Sham Point. eCAM 2014: 1-6.
15. Shin KM, Park JE, Lee S, Choi SM, Ahn YC, Lee JW, et al. Effect of Siguan Acupuncture on Gastrointestinal Motility: A Randomized, Sham-Controlled, Crossover Trial. EeCAM 2013: 1-7.
16. K Maheshkumar, B Deenadayalan, A Akila, V Venugopal, S Poonguzhali. Effectiveness of taichong (LR3) acupuncture point on blood pressure in patients with hypertension: A randomized sham control trial. AIMED 2021; 8(1): 58-62.
17. Jun MH, Kim YM, Kim JU. Modern acupuncture-like stimulation methods: a literature review. Integr Med Res 2015; 4(4): 195-219.
18. Larson JD, Gutowski KA, Marcus BC, Rao VK, Avery PG, Stacey DH, et al. The Effect of Electroacustimulation on Postoperative Nausea, Vomiting, and Pain in Outpatient Plastic Surgery Patients: A Prospective, Randomized, Blinded, Clinical Trial. Plastic and Reconst Surg 2010; 125(3): 989-94.
19. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. Psychiatry Investig 2018; 15(3): 235-45.
20. Taelman J, Vandeput S, Spaepen A, Van Huffel S, et al. Influence of Mental Stress on Heart Rate and Heart Rate Variability. Springer Berlin Heidelberg 2009;1366-9.
21. Fang SC, Wu YL, Tsai PS. Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: a meta-analysis of cohort studies. Biol Res For Nursing 2020; 22(1): 45-56.
22. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science, 1981; 213(4504): 220-2.
23. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043-65.
24. Thielmann B, R Pohl, I Böckelmann. Heart rate variability as a strain indicator for psychological stress for emergency physicians during work and alert intervention: a systematic review. J Occup Med Toxico 2021; 16(1): 24.
25. Ibáñez V, Silva J, Cauli O. A survey on sleep assessment methods. PeerJ 2018; 6(25): e4849.
26. Gilgen-Ammann R, Schweizer T, Wyss T. RR interval signal quality of a heart rate monitor and an ECG Holter at rest and during exercise. Eur J Applied Physiol 2019; 119(7): 1525-32.
27. Schaffarczyk M, Rogers B, Reer R, Gronwald T. Validity of the Polar H10 Sensor for Heart Rate Variability Analysis during Resting State and Incremental Exercise in Recreational Men and Women. Sensors, 2022; 22(17): 6536.
28. Snedecor, G.W. and Cochran, W.G. Statistical Methods, eight edition. Iowa state University press, Ames, Iowa, 1989: 1191.
29. Wu JH, Chen HY, Chang YJ, Wu HC, Chang WD, Chu YJ, et al. Study of autonomic nervous activity of night shift workers treated with laser acupuncture. Photomed Laser Surg 2009; 27(2): 273-9.
30. Jesus FG, Duque AP, Sant C, Massolar A, Lopes GPF, Carvalho ACA, et al. Transcutaneous Electrical Nerve Stimulation of PC5 and PC6 Acupoints Increases Sympathovagal Balance but Not Oxidative Stress in Healthy Subjects: A Randomized Clinical Trial. JAMS 2021; 14(5): 183-92.

31. Sparrow K, Golianu B. Does Acupuncture Reduce Stress Over Time? A Clinical Heart Rate Variability Study in Hypertensive Patients. Med Acupunct 2014; 26(5): 286-94.
32. Haker E, Egekvist H, Bjerring P. Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects. Journal of the Autonomic Nervous System 2000; 79(1): 52-9.
33. Nishijo K, Mori H, Yosikawa K, Yazawa K. Decreased heart rate by acupuncture stimulation in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerve. Neurosci Lett 1997;227(3):165-8.
34. Lee SY, Baek YH, Park SU, Moon SK, Park JM, Kim YS, et al. Intradermal acupuncture on shen-men and nei-kuan acupoints improves insomnia in stroke patients by reducing the sympathetic nervous activity: a randomized clinical trial. Am J Chin Med 2009; 37(6): 1013-21.
35. Chiou YF, Yeh ML, Wang YJ. Transcutaneous Electrical Nerve Stimulation on Acupuncture Points Improves Myofascial Pain, Moods, and Sleep Quality. Rehabil Nurs 2020; 45(4): 225-33.
36. Song B, Chang Y, Li Y, Zhu J. Effects of Transcutaneous Electrical Acupoint Stimulation on the Postoperative Sleep Quality and Pain of Patients After Video-Assisted Thoracoscopic Surgery: A Prospective, Randomized Controlled Trial. Nature and Science of Sleep 2020; 12: 809-19.
37. Spence DW, Kayumov L, Chen A, Lowe A, Jain U, Katzman MA, et al. Acupuncture Increases Nocturnal Melatonin Secretion and Reduces Insomnia and Anxiety: A Preliminary Report. JNCN 2004; 16(1): 19-28.
38. Li C, Wang Y, Li B, Su S. Comparative study on effect of acupuncture at neiguan (pc6) and shenmen (ht7) acupoints on brain wave of sleep deprivation model rats. Hubei J TCM 2017; 39(6): 13–6.

ORIGINAL ARTICLE

Evaluation of educational intervention on knowledge and awareness regarding glaucoma among working adults in northeast of Malaysia

Wen Khang Chong, MMed[1,2], Daniel Sen Kai Phang, MMed[1,2], Ibrahim Mohd-Ismail, MMed[3], Ab Hamid Siti-Azrin, MBBS[4], Ahmad Tajudin Liza-Sharmini, MMed PhD[1], Yaakub Azhany, MMed, PhD[1]

[1]Department of Ophthalmology and Visual Sciences, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia, [2]Department of Ophthalmology, Hospital Umum Sarawak, 93586 Kuching, Sarawak, Malaysia, [3]Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia, [4]Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: To determine the level of good awareness and knowledge on glaucoma and their associated factors as well as the effectiveness of the glaucoma educational intervention among the working adults in northeast of Malaysia.

Materials and methods: Participants from the governmental departments were recruited and divided into intervention group and control group. A translated and validated questionnaire on awareness and knowledge related to glaucoma were used. Educational interventions were given for both groups. Post-test assessments were completed at one month and three months post intervention.

Results: A total of 202 participants enrolled for the study (102 intervention group and 100 control group). 64.9% of the participants were aware of glaucoma and 49% of the participants had good knowledge score on glaucoma. Higher educational attainments (bachelor and diploma holders) were the only factors significantly associated with good glaucoma knowledge (p <0.001). There was significant increase in the proportion of good glaucoma knowledge in the intervention group one month after the educational intervention (p < 0.001) and the effect persisted after three months (p < 0.003). There was also significantly higher proportion of good post-test glaucoma knowledge between intervention and control group (p = 0.003).

Conclusion: Although the public was well aware of glaucoma, there was relatively little understanding of the condition. Educational interventions can be effective to bridge the gap in promoting the glaucoma awareness and better understanding of glaucoma.

KEYWORDS:
Glaucoma awareness, Glaucoma knowledge, educational intervention

INTRODUCTION

One of the important aspects of public health measures is raising awareness and information about a particular condition. It aims to increase knowledge and consciousness about specific diseases, risk factors, prevention measures, and health promotion initiatives by disseminating evidence-based information. Low health literacy hinders patients from comprehending the severity of a disease and the preventive measures as well as treatment options available for decision making.[1] The level of awareness and understanding of several communicable and non-communicable diseases has been found to be significantly lacking in numerous research.[2-7]

Glaucoma is an ocular disease with the hallmarks characterized by chronic, progressive optic neuropathy associated with structural damage to the optic nerve and resulting visual field abnormalities.[8-10] Glaucoma is frequently referred to as the "thief of sight" because it normally causes no symptoms in the early stages of the disease but may progresses and eventually lead to blindness if untreated. Glaucoma is one of the major causes of blindness on a global scale; it is estimated to affect approximately 90 million people worldwide, and the number is increasing.[11-13] While in Malaysia, glaucoma is reported to be the third most prevalent cause of blindness, accounting for 6.6% of all cases of blindness, following untreated cataract and diabetic retinopathy.[14] Poor adherence to therapy and life-long clinic follow-ups are acknowledged as barriers to successful treatment.

Patients' ignorance about the glaucoma disease is one of several variables linked to treatment failure.[15] With early glaucoma diagnosis and prompt administration of effective treatment, progression of the disease and blindness can be averted. Various studies have been conducted to evaluate the level of awareness and knowledge of the patients as well as general population in different geographical locations.[16-20] The glaucoma awareness level was found to be between 61.3% and 68.9%. The effectiveness of educational intervention in raising the knowledge of glaucoma was also demonstrated in a few studies.[21-22] In this study, we aim to evaluate the level of awareness and knowledge regarding glaucoma among adults in northeast of Malaysia. as well as the effectiveness of glaucoma education intervention.

This article was accepted: 16 September 2024
Corresponding Author: Azhany Yaakub
Email: azhany@usm.my

MATERIALS AND METHODS

Subjects

This study was approved by the Universiti Sains Malaysia Ethical Committee (USM/JEPeM/21020150) and was conducted in accordance with World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. The confidentiality of the data was strictly safeguarded. A quasi-experimental study was conducted between 1st June 2021 and 31st December 2022. A total of 202 subjects were recruited. The sample size was calculated using G power software version 3.9.4 using a two proportional comparison formula. The sampling method was simple random sampling. The Malaysian government officers in Kota Bharu, Kelantan were recruited according to inclusion and exclusion criteria. The inclusion criteria include adults aged between 25-55 years old who were working in Malaysian government sectors. The exclusion criteria include those who were healthcare-related staff or with the confirmed diagnosis of glaucoma. Those who were unable to participate in both pre and post-test questionnaire were also excluded from the study. The participations were voluntary and informed consents were obtained prior to the study. The subjects were divided into interventional group and control group. To avoid sample contamination, intervention group comprised subjects from the government departments located in Kota Bharu Federal Building, whilst the control group was consisted of the subjects from Kota Bharu Municipal Council.

Translation and Validation of Questionnaire

*This study involved using a validated questionnaire as self-*administered online survey and an educational intervention in the form of a short video, a brief lecture, and a brochure to the government officers in Kota Bharu, Kelantan. The questionnaire to evaluate the glaucoma awareness and knowledge among working adults in Kelantan was adapted from Baker et. al.[23] and was translated into Malay language through the stages which follows the guideline.[24] Forward translation of the questionnaire was performed by three independent translators who are proficient in both English and Malay language. A committee team comprised lecturers from department of Ophthalmology, Community Medicine, and Biostatistics, as well as ophthalmology trainees were involved in the process of review and reconciliation of the forward translation. The back translation of the questionnaire from Malay language to English was then performed by four translators which consisted of four ophthalmologists who are fluent in both languages. The committee team was then involved in the harmonization, proofreading and finalization of the translated questionnaire.

The glaucoma knowledge questionnaire consisted of 14 items. The questionnaire was self-administered and the dichotomous-scale items in the questionnaire were analyzed using a two-parameter logistic model of item response theory (2-PL IRT). Analysis of the questionnaire showed good psychometric properties. The discrimination and difficulty index were good. Regarding the difficulty parameter, all the knowledge items in the questionnaire were within the acceptable range of –3 to +3. For discrimination, most of the items in the questionnaire were within the acceptable range of 0.35 to 2.5. The item goodness-of-fit showed that 14 of the items did fit well (p =0.054). The amount of total information trapped by the items between the -3 to +3 ranges of ability was 99.0%. Internal consistency by marginal reliability was 0.91.

Data Collection

Glaucoma Awareness and Knowledge questionnaires including the sociodemographic information were distributed in the form of Google Forms online system via email. A comprehensive summary of the study was presented, and a consent form was signed before proceeding to the questionnaire. This was a self-administered questionnaire; the data was then recorded for further analysis. Awareness was considered present when a participant had heard of or knows the existence of glaucoma. Each glaucoma knowledge question was given one mark if answered correctly, zero mark if the answer was incorrect or unsure. If a participant answered seven or more questions correctly, he or she was considered to have good glaucoma knowledge.

Educational Intervention

Educational intervention was conducted by presenting a short video, a lecture, and a brochure to the participants after they had completed the pre-test questionnaire. For the interventional group, the educational intervention consisted of a two-minute video on glaucoma information, a 30-minute slides presentation by the Glaucoma consultant as well as a brochure with the general information in glaucoma. The sessions of video and lecture presentations were conducted via online using Webex by Cisco. The same questionnaire was then completed by the same subjects one month and three months after the sessions of educational intervention. Nevertheless, for the control group, the subjects received 30-minute slide presentations on cataract by an ophthalmologist. The sessions of slide presentations were conducted via online using Google Meet and similar questionnaire was then completed by the same subjects one month and three months after the sessions.

Statistical Analysis

Data were analysed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). All data was entered and checked for incomplete entry and double entry using SPSS version 27.0. For the descriptive statistics data, numerical variables were presented by means (standard deviations) and categorical variables were presented in frequency (percentage). We used comparative statistic to examine the potential association between sociodemographic factors and glaucoma awareness as well as the high level of glaucoma knowledge. Simple logistic regression and multiple logistic regression were used to in our study to evaluate for the association. The McNemar's test was used to determine the difference on the proportion of subjects with good glaucoma knowledge scores between pre-intervention, one-month post-intervention and three-month post intervention. To ensure the normal distribution of the sample, central limit theorem (CLT) was used which as the sample size increases, the distribution of the sample means approximates a normal distribution. The sample size equal or greater than 30 are often considered to fulfill the CLT. P-value <0.05 was considered statically significant for all statistical analyses.

Table I: Demographic characteristics of the participants (n=202)

Sociodemographic features	Interventional group n (%)	Control group n (%)	P value
Gender			
Male	42 (41.2)	28 (28.0)	0.049 [a]
Female	60 (58.8)	72 (72.0)	
Age* (years)	40.43 ± 5.22	39.95 ± 5.16	0.510 [b]
Ethnicity			
Malay	101 (99.0)	100 (100.0)	0.505 [c]
Non-Malay	1 (1.0)	0 (0.0)	
Marital Status			
Single	6 (5.9)	22 (22.0)	0.001 [a]
Married	96 (94.1)	78 (78.0)	
Highest Education Level			
Secondary	38 (37.3)	32 (32.0)	0.535 [a]
Diplom[a]	21 (20.6)	18 (18.0)	
Bachelor and above	43 (42.1)	50 (50.0)	
Household Income			
B40	31 (30.4)	39 (39)	0.083 [c]
M40	70 (68.6)	56 (56)	
T20	1 (1.0)	5 (5)	
Medical co-morbidities			
Yes	29 (28.4)	31 (31.0)	0.690 [a]
No	73 (71.6)	69 (69.0)	
Other ocular disorders			
Yes	27 (26.5)	23 (23.0)	0.568 [a]
No	75 (73.5)	77 (100.0)	
Family history			
Yes	6 (5.9)	7 (7.0)	0.746 [a]
No / Unsure	96 (94.1)	93 (93.0)	

[a] Pearson chi-square, [b] independent t-test, [c] Fisher Exact test
*Mean (SD)

Table II: Determinants of good awareness of glaucoma

Variables	B (S.E)	Crude OR (95%)	P value
Age	-0.03 (0.03)	0.98 (0.92, 1.03)	0.382
Gender			
Male*			
Female	-0.04 (0.31)	0.96 (0.53, 1.77)	0.902
Marital status			
Single*			
Married	-0.21 (0.42)	0.81 (0.36, 1.85)	0.622
Highest Education level			
Secondary*			
Diploma	-0.07 (0.41)	0.94 (0.42, 2.09)	0.875
Bachelor and above	-0.44 (0.33)	0.65 (0.34, 1.24)	0.189
Household income			
B40*			
M40	0.23 (0.32)	1.26 (0.67, 2.34)	0.474
T20	0.78 (0.86)	2.18 (0.41, 11.68)	0.362
Medical co-morbidities			
Yes*			
No	-0.30 (0.32)	0.74 (0.40, 1.39)	0.349
Presence of other eye diseases			
Yes*			
No	0.07 (0.34)	1.07 (0.55, 2.10)	0.845
Previous eye screening			
Yes*			
No	0.25 (0.71)	1.28 (0.32, 5.11)	0.727

Values are presented as OR (95%CI). By multiple logistic regression model
Note: b, regression coefficient; OR ,odds ratio; CI, confidence interval
*used as reference category
Significant results (p-value < 0.05)

Table III: Determinants of good glaucoma knowledge scores at 1 month post intervention

Variables	B (S.E)	Crude OR (95%)	P value
Age	-0.05 (0.03)	0.95 (0.90, 1.01)	0.088
Gender			
Male*	0	1	
Female	-0.41 (0.30)	0.66 (0.37, 1.19)	0.166
Marital status			
Single*	0	1	
Married	-0.21 (0.41)	0.81 (0.36, 1.80)	0.603
Highest Education level			
Secondary*	0	1	
Diploma	1.66 (0.44)	5.27 (2.24, 12.41)	<0.001
Bachelor and above	1.94 (0.36)	6.99 (3.43, 14.27)	<0.001
Household income			
B40*	0	1	
M40	0.72 (0.31)	2.05 (1.13, 3.73)	0.019
T20	1.22 (0.90)	3.39 (0.58, 19.78)	0.176
Medical co-morbidities			
Yes*	0	1	
No	-0.15 (0.31)	0.86 (0.47, 1.57)	0.624
Presence of other eye diseases			
Yes*	0	1	
No	-0.05 (0.33)	0.95 (0.50, 1.80)	0.872
Family history of glaucoma			
Yes*	0	1	0.184
No / Unsure	-0.82 (0.62)	0.44 (0.13, 1.48)	
Previous eye screening			
Yes*	0	1	0.479
No	-0.47 (0.66)	0.63 (0.17, 2.29)	
Intervention			
No*	0	1	
Yes	0.84 (0.29)	2.33 (1.32, 4.09)	0.003

Values are presented as OR (95%CI). By Simple logistic regression
Note: b, regression coefficient; OR, odds ratio; CI, confidence interval
*Used as reference category
Significant results (p-value < 0.05)

Table IV: Factors associated with good glaucoma knowledge scores at 1 month post intervention

Factors	B (SE)	Adjusted OR (95% CI)	p-value
Intervention			
No*	0	1	
Yes	1.09 (0.31)	2.96 (1.60, 5.48)	<0.001
Eye Screening			
No*	0	1	
Yes	2.34 (1.13)	10.41 (1.13, 96.03)	0.039
Education level			
Secondary*	0	1	
Diploma	0.81 (0.43)	2.24 (0.97, 5.18)	0.060
Bachelor and above	1.37 (0.36)	3.95 (1.96, 7.94)	<0.001

Values are presented as OR (95%CI). By Multiple logistic regression. Backward LR method applied
Note: b, regression coefficient; OR, odds ratio; CI, confidence interval
*Used as reference category
Significant results (p-value < 0.05)

RESULTS

Demographic Features

There were 202 participants recruited in this study. 102 (50.5%) subjects were assigned to the interventional group while 100 (49.5%) subjected were in the control group. The mean ages of the interventional and control groups were 40.43 (SD ± 5.22) and 39.95 (SD ± 5.18), respectively. There were more women than men in both groups. Majority of the participants are of Malay ethnicity and Muslims (99.5%). Most of the respondents were married (86.1%).

The majority of the participants attained a degree or higher as their highest attained academic qualification. As classified based on the Household Income and Basic Amenities survey of 2019, Department of Statistics, Malaysia, household income can be classified into three categories: B40, M40, and T20. B40 represents the bottom 40% with a monthly household income of RM 4850 (approximately USD 1,030) or less. M40 represents the middle 40%, which means a household income of RM 4851–RM 10,970 (approximately USD 1,030-2,334). T20 represents the top 20% which earns a monthly household income more than RM 10,970

(approximately USD 2,334). Majority of participants were in the M40 category.

Approximately three quarters of the participants had no ocular disorders diagnosed previously. The main complaints from those with ocular disorders were refractive errors (94%). Apart from that, there were three participants with allergic conjunctivitis, retinal detachment, and giant cell arteritis, respectively. The sociodemographic characteristics of the participants were summarized in Table I.

Awareness about Glaucoma

There were 64.9% participants out of the total 202 who were aware of glaucoma. Prior to the educational intervention, 60.8% from intervention group were aware of glaucoma while 69% from the control group had heard of glaucoma previously.

5.3% participants out of 131 who were aware of glaucoma had attended eye screening previously. 9.9% out of 131 participants who had awareness regarding glaucoma had positive family history of glaucoma. Conversely, those were not aware of glaucoma did not have family history of glaucoma. However, no significant association between the demographic features and good awareness of glaucoma was found in this study using simple and multiple logistic regression tests as shown in table II. The main sources of information of glaucoma reported were social media and internet (72.5%), followed by printed material such as magazines, newspapers, and pamphlets (47.3%). However, only 7 out of 10 participants who had joined eye screening programme previously knew about glaucoma.

Knowledge about Glaucoma

There were 49% out of a total of 202 participants had good glaucoma knowledge before the intervention. Out of 99 participants with good glaucoma knowledge, 47.5% were in the interventional group while 52.5% were in the control group. The level of education was strongly associated with good knowledge of glaucoma. Simple logistic regression test showed that there were 5.27 and 6.99 higher odd ratio to have good glaucoma knowledge for those who attained Diploma and bachelor education respectively, as compared to those who completed secondary education ($p < 0.001$). Participants who were in the M40 group were found to have 2.05 higher odd ratio to have good glaucoma knowledge score than those in B40 group ($p < 0.019$).

Multiple logistic regression showed that intervention group, eye screening and university education level were significantly associated with good glaucoma knowledge score as shown in Table IV. Those with intervention had 2.96 higher odd to have good glaucoma knowledge compared to those without intervention after controlling for eye screening and education level. Those with eye screening had a 10.41 higher odd to have good glaucoma knowledge compared to those without eye screening after controlling for intervention and education. Those with bachelor and above education level had a 3.95 higher odd ratio to have good glaucoma knowledge compared to those in secondary education after controlling for intervention and eye screening.

Educational intervention on glaucoma knowledge score

There was an increase of proportion of participants in intervention group who had good knowledge score from pre-intervention (n = 47, 46.1%) to one month (n = 68, 66.7%) and three months (n = 64, 63.7%) post educational intervention. The statistical analysis using exact McNemar's test determined that there was a statistically significant difference in the proportion of those with good glaucoma knowledge score between pre- and one-month post-intervention ($p < 0.001$) as well as between pre- and three months post intervention ($p = 0.003$). No statistical significance was found in the proportion of good glaucoma knowledge between one month post- and three months post-intervention ($p = 0.541$).

In the control group, the proportion of participants with good glaucoma knowledge score were 52% pre-intervention, 46% at one-month post-intervention and 42% at three months post intervention. The exact McNemar's test showed that no significant difference in the proportion of good glaucoma knowledge among pre-, one month post- and three months post-intervention in the control.

However, there was significant difference between intervention group and control group in term of proportion of good glaucoma knowledge at one month post and three months post-intervention ($p = 0.003$). Higher proportion of participants with good glaucoma knowledge score was noted in the intervention group one month and three months after the educational intervention, as compared to control group. Table 5 showed the comparison of glaucoma knowledge score pre-intervention and 3-month post intervention.

DISCUSSION

Multiple factors including poor awareness and understanding of glaucoma have been identified to be the leading causes of late presentation and treatment failure in glaucoma.[25] High levels of awareness and understanding are essential for the early diagnosis and treatment of glaucoma to prevent irreversible blindness. Various surveys on glaucoma awareness and knowledge showed that there are significant gaps in glaucoma patients.[26] Public health education interventions have been shown to be effective in changing behaviour in healthcare utilisation by increasing awareness and knowledge of a variety of ophthalmic and non-ophthalmic diseases.[27-30] Emphasis on the necessity and importance of eye health education should be in place to reduce the social and economic burdens caused by glaucoma.

In this study, there was generally high level of awareness of glaucoma among the participants (64.9%). Similar results were also observed in other studies from other developing countries with awareness level ranged from 61.3% to 68.9%.[16-20] However, a local population study conducted by Chew et al. in 2004 revealed that the glaucoma awareness level was 71.5% among non-medical academic staff in a Malaysian university.[31] A study by Gasch et al. also showed higher glaucoma awareness of 72% which was higher than our study.[32] The higher glaucoma awareness observed was possibly because the population surveyed was composed of individuals from urban metropolitan area with a high level of education and better access to public health information.

Interestingly, those with positive family history of glaucoma were all aware of the existence of glaucoma in this study. The contact with family members who are glaucoma patients is the significant contributor to the glaucoma awareness among the population ($p<0.001$). In contrary to other studies in which there were associations were noted in glaucoma awareness with younger age, higher educational attainment, positive family history and previous eye screening.[18-19] There were no significant associations between the sociodemographic features and the level of awareness observed in our study. This may be accounted for by the small age range of the participants in our study, which excluded children and the elderly. Only a minority of the participants in the study had undergone eye screening previously evidenced by wider 95% CI in our results. This small number had no impact on the study's statistical significance. The high awareness of glaucoma may be attributed to easy access to the internet and mass media, which were the primary sources of information on glaucoma in this study.

Despite relatively high glaucoma awareness among the participants in this study, the overall understanding of the disease is still lacking. Approximately 50% of the study participants attained good glaucoma knowledge score. Similarly to our findings, other studies also produced comparable outcomes.[17-20] This finding would indicate that awareness of glaucoma does not necessarily translate into actual understanding of the condition. Our study found that the only factor associated with good glaucoma knowledge was highest educational attainment. Similar to numerous studies, a higher level of education is linked to a greater understanding of glaucoma.16-19 Nonetheless the other factors such as younger age, family history of glaucoma, higher income and previous eye screening were not significantly related to good knowledge on glaucoma. This emphasizes the significance of glaucoma education being disseminated among the population, regardless of a person's sociodemographic background.

Our present study showed a significant increase in the proportion of participants with good knowledge of glaucoma one month and three months after the educational intervention. This beneficial impact of educational was shown to persist from one month to three months post-intervention. The significant improvement seen in the intervention group in terms of the proportion of good glaucoma knowledge stood in contrast to the control group. There were various studies conducted to evaluate the efficacy of an educational intervention on improving the knowledge for glaucoma patients.[26] In the analysis, various methods of educational interventions including videotape presentation and brochures, interactive and didactic approach as well as nurse-patient interaction in the waiting room were examined. Despite the variations on the methods of conducting educational intervention, all the studies showed a significant increase in the glaucoma knowledge score after educational intervention, demonstrating the potential of education as a tool for promoting awareness and understanding of this important eye disease.

Most studies were performed on individuals who had glaucoma; however, there are relatively few studies that examine how education affects public understanding and awareness of glaucoma, which is crucial for promoting early detection and successful treatment of glaucoma. The educational workshops were conducted along with Philadelphia Glaucoma Detection and Treatment Project in the United States of America (USA) to assess the impact of education intervention using pre-test and post-test questionnaires and 30-minute presentation.[21] There was a significant increase in the composite scores of glaucoma questionnaire after the workshops, however only one third of the participants who attended the educational workshop scheduled and attended glaucoma screening examinations.[21] Interestingly, the response rate for eye screening following the educational session is still unsatisfactory, necessitating more research into the causes of the low response rate to screening and potential solutions.

In the age of technological advancement, electronic devices such as mobile phones and computers have become an essential tool in public health education. In a Chinese study done by Li et. al., it demonstrated that mobile-based education was remarkably effective in increasing public understanding of glaucoma.[22] Similarly, our study used online platform to conduct the lectures and video presentations for the educational intervention, we found that it is equally effective in increasing the level of glaucoma knowledge among the participants. There is an increase in awareness among our control group towards ophthalmic diseases which increased their understanding on ophthalmic related diseased. Having access to internet enables our control participants to better understand other ophthalmic diseases especially glaucoma. Minimum reduction in percentage is expected from the samples because it was about retained knowledge after certain period of time. However, the reduction is not significant. Similar observations were seen in other knowledge and awareness studies.[21]

There are several limitations of the study that should be acknowledged. Firstly, this is a single centre study which may limit the generalizability of the results to other populations in Malaysia. Moreover, the study relied on self-reported data, which is subject to bias and may not accurately reflect actual knowledge and awareness levels. Furthermore, the study had only follow-up for three months after the educational intervention, it may be difficult to determine if the intervention had a sustained impact on glaucoma knowledge and awareness. Ongoing research in this area would be beneficial to comprehend the implications of education and other factors on glaucoma knowledge and awareness as well as its impact on attitude changes in the population towards the disease that promote seeking regular eye examinations and adhering to the treatment recommendations.

Currently there is no standardized questionnaires that adequately assess the awareness and knowledge about glaucoma in a general population. There was considerable variability in the development as well as the format of the glaucoma questionnaires which were presented in the form of open-ended questions, close-ended questions or both.[26] Our questionnaire was adapted and translated from previous study by Baker et. al. which consisted of 14 self-administered, close-ended questions. 23 Rigorous review of translated questionnaire by a panel of experts including glaucoma specialist, ophthalmologists, community medicine

consultant and medical biostatistics lecturer was conducted. Our questionnaire contained only 14 items, which may not cover many relevant aspects of knowledge and awareness of glaucoma. Despite these limitations, we believe the design and method of this study were reliable. The strength of our study is the suitability of the questionnaire to our local Malaysian population as it eradicated the language barrier in assessing the depth of understanding towards glaucoma.

CONCLUSION

There are still significant gaps in awareness and knowledge about glaucoma in the public, this present study provides valuable insights into the impact of educational intervention on improving knowledge and awareness of glaucoma significantly. Therefore, education is an important tool for promoting eye health and preventing visual impairment.

ACKNOWLEDGEMENT

We would like to express gratitude to the heads of department of the Governmental departments in Kota Bharu, Kelantan for granting the permission to conduct this study.

REFERENCES

1. Teo CL, Chee ML, Koh KH, Tseng RMWW, Majithia S, Thakur S, et al. COVID-19 awareness, knowledge and perception towards digital health in an urban multi-ethnic Asian population. Sci Rep 2021; 11: 1–13.
2. Zheng YB, Shi L, Gong YM, Wang XX, Lu QD, Que JY, et al. Public awareness and knowledge of factors associated with dementia in China. BMC Public Health 2020; 20: 1–9.
3. Johnson EJ, Hariharan S. Public health awareness: knowledge, attitude and behaviour of the general public on health risks during the H1N1 influenza pandemic. J Public Health 2017; 25: 333–7.
4. Parsons Leigh J, Brundin-Mather R, Moss SJ, Nickel A, Parolini A, Walsh D, et al. public awareness and knowledge of sepsis: a cross-sectional survey of adults in Canada. Crit Care 2022; 26: 1–12.
5. Hady AFA, Farag HM, Sheikhany AR. The awareness and knowledge of dysphagia among health care practitioners in Egypt. Egypt J Otolaryngol 2023; 39: 25
6. Sahu DP, Subba SH, Giri PP. Cancer awareness and attitude towards cancer screening in India: A narrative review. J Family Med Prim Care 2020; 9: 2214–8.
7. Selvarajoo S, Liew JWK, Tan W, Lim XY, Refai WF, Zaki RA, et al. Knowledge, attitude and practice on dengue prevention and dengue seroprevalence in a dengue hotspot in Malaysia: A cross-sectional study. Sci Rep 2020; 10: 1–13.
8. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: A review. Jama 2014; 311: 1901–11.
9. Cantor L, Rapuano C, Cioffi G. 2017-2018 Basic and Clinical Science Course: Glaucoma. Am Acad Ophthalmol 2018; 1–16.
10. Broadway DC. Visual field testing for glaucoma – a practical guide. Community Eye Heal J 2012; 25: 66–70.
11. Bourne RA, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, et al. Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob Heal 2013; 1: 339–49.
12. Wang HW, Sun P, Chen Y, Jiang LP, Wu HP, Zhang W, et al. Research progress on human genes involved in the pathogenesis of glaucoma (Review). Mol Med Rep 2018; 18: 656–74.
13. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol 2012; 96: 614-618.
14. Chew FLM, Salowi MA, Mustari Z, Husni MA, Hussein E, Adnan TH, et al. Estimates of visual impairment and its causes from the national eye survey in Malaysia (NESII). PLoS One 2018; 13: 1–11.
15. Newman-Casey PA, Weizer JS, Heisler M, Lee PP, Stein JD. Systematic review of educational interventions to improve glaucoma medication adherence. Semin Ophthalmol 2013; 28: 191–201.
16. Zhang B, Gao JG, Pan C, Luan M, Chen XM. Awareness and knowledge about cataract, glaucoma, and age-related macular degeneration in Chengdu, China. Int Eye Sci 2016; 16: 397–402.
17. Kizor-Akaraiwe NN, Monye HI, Okeke S. Awareness and knowledge about glaucoma and proportion of people with glaucoma in an urban outreach programme in Southeast Nigeria. BMJ Open Ophthalmol 2017; 1: 1–10.
18. Nujaim H, Mohammed H. Awareness and knowledge of glaucoma among the general Saudi public. IAIM 2018; 5: 107–10.
19. Dağtekin G, Demirtaş Z, Soysal A, Yildirim N, M. Önsüz F, Metintaş S. The assessment of the knowledge and awareness about glaucoma in glaucoma patients and general population: a sample from Turkey. Int J Res Med Sci 2017; 6: 35-41.
20. Alemu DS, Gudeta AD, Gebreselassie KL. Awareness and knowledge of glaucoma and associated factors among adults: A cross sectional study in Gondar Town, Northwest Ethiopia. BMC Ophthalmol 2017; 17: 1–12.
21. Johnson DM, Stratford S, Shyu AP, Sembhi H, Molineaux J, Reamer C, et al. The impact of educational workshops on individuals at risk for glaucoma in the Philadelphia Glaucoma Detection and Treatment Project. Patient Educ Couns 2016; 99: 659–64.
22. Li J, Huang W, Gao J, Li D, Xu L, Huang J. Impact of Mobile-Based Health Education on the Awareness and Knowledge of Glaucoma in Chinese Patients. Telemed J E Health 2019; 25: 455–61.
23. Baker H, Murdoch IE. Can a public health intervention improve awareness and healthseeking behaviour for glaucoma? Br J Ophthalmol 2008; 92: 1671–5.
24. Wild D, Grove A, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. Value Health 2005; 8: 94–104.
25. Siti-Azrin A.H, Anis K.G, Mohd I.I, Chong W.K, Mangalathevi Y, Faisal A, Liza-Sharmini A.T, Azhany Y. Validation of Malay version questionnaire on knowledge on glaucoma among community in Malaysia 2024. (Manuscript in preparation).
26. Peralta E, Muir KW, Rosdahl JA. Systematic Review of Knowledge Assessments for Glaucoma Patients. Semin Ophthalmol 2018; 33: 377-388.
27. Gopu GS, Rao VB, Vadivet J. Impact of health education on the knowledge of tuberculosis among sputum-positive pulmonary TB patients and their care-givers. Nurs J India 2012; 103: 160–2.
28. Zühlke LJ, Engel ME. The Importance of Awareness and Education in Prevention and Control of RHD. Glob Heart 2013; 8: 235–9.
29. Poureslami I, Nimmon L, Doyle-Waters M, Rootman I, Schulzer M, Kuramoto L, et al. Effectiveness of educational interventions on asthma self-management in Punjabi and Chinese asthma patients: a randomized controlled trial. J asthma 2012; 49: 542–51.
30. Shah M. Glaucoma Education Intervention: Using a Trained Volunteer to Improve Patient Understanding and Compliance. Int J Ophthalmol Vis Sci 2018; 3: 27-31.
31. Chew YK, Reddy SC, Karina R. Awareness and knowledge of common eye diseases among the academic staff (non-medical faculties) of University of Malaya. Med J Malaysia 2004; 59: 305–11.
32. Gasch AT, Wang P, Pasquale LR. Determinants of glaucoma awareness in a general eye clinic. Ophthalmology 2000; 107: 303–8.

IL-41: A novel serum marker correlates with disease activity in patients with ankylosing spondylitis

Baneen Mueen Ali, MSc[1], Inas K Sharquie, PhD[1], Faiq I Gorial, FIBMS[2]

[1]Department of Microbiology & Immunology, College of Medicine, University of Baghdad, Baghdad, Iraq, [2]Department of Medicine, College of Medicine, University of Baghdad, Iraq

ABSTRACT

Introduction: Interleukin (IL)-41, a type of cytokine also known as Metrnl, is involved in the pathogenesis of various inflammatory and immune-related diseases. However, its role in Ankylosing Spondylitis (AS), a field yet to be explored, remains a mystery. This study therefore assesses the diagnostic utility of IL-41 in patients with AS and examines the correlations among IL-41 levels, disease activity, and patients' demographic and clinical data. Such novel insights could have significant implications for the diagnosis and management of AS.

Materials and methods: Eighty-eight patients diagnosed with AS were enrolled from the Rheumatology Unit at Baghdad Teaching Hospital. Participants were categorized into two groups based on disease status: inactive (n = 44) and active (n = 44). Additionally, 44 matched healthy individuals were included as controls. Comprehensive medical histories were obtained, including disease duration, body mass index, sex, and age. Laboratory parameters related to the disease—such as C-reactive protein, human leukocyte antigen (HLA-B27), and rheumatoid factor—were also measured. Serum IL-41 levels were quantified using an enzyme-linked immunosorbent assay.

Results: The study revealed a significant difference in levels of IL-41 in patients with AS (17.721±0.705 ng/L) compared to controls (8.495±0.984 ng/L; P = 0.009). The mean serum IL-41 concentration was highest in the active group (23.037±5.268 ng/L), followed by the inactive group (12.411±1.672 ng/L; p = 0.001) and controls (8.495±0.984 ng/L). Serum IL-41 levels demonstrated strong validity for diagnosing AS, with a cut-off value of ≥ 9.35 ng/mL and an area under the curve of 0.991. The sensitivity, specificity, and accuracy were 97.7%, 79.5%, and 92.38%, respectively (p = 0.002).

Conclusions: IL-41 is a potential new diagnostic biomarker for AS and associated with patient's disease activity. These insights could potentially transform the way we diagnose and manage AS, offering new avenues for improved patient care and outcomes.

KEYWORDS:
Ankylosing Spondylitis, Interleukin-41, Autoimmune disease, HLA-B27, Disease activity

INTRODUCTION

Ankylosing Spondylitis (AS) is a common inflammatory autoimmune disease primarily targeting spine joints that leads to severe and chronic pain, and in severe cases, vertebrae fusion.[1-3] Diagnosis of AS can be challenging due to the wide range of non-specific, musculoskeletal and extra-articular symptoms associated with the disease. The development of more effective and specific diagnostic tools has been limited, partly due to the limited knowledge of AS pathogenesis.[1]

While pathogenesis remains unclear, AS has been associated with aberrant immune cell function. Consequently, the biochemical markers responsible for mediating immune interactions and cell communications have been investigated.[3] The biochemical parameters for AS diagnosis published by NICE (National Institute for Health and Care Excellence) include human leukocyte antigen (HLA)-B27 levels.[4] In addition, elevated levels of pro-inflammatory cytokines and anti-inflammatory cytokine activity have been associated with vital inflammatory processes in AS.[1,5-6] However, little is known about the association between AS and interleukin (IL)-41, which is the focus of this study.

Interleukins, a type of cytokine, are frequently used as biomarkers to track disease progression and various conditions. Specific interleukins have shown potential in diagnosing and monitoring various diseases. For instance, IL-37 is a potential diagnostic biomarker for juvenile idiopathic arthritis, and IL-39 and IL-40 have been linked to rheumatoid arthritis, autoimmune thyroid disease, and systemic lupus erythematosus.[7-12] IL-6 is involved in rheumatoid arthritis and systemic lupus erythematosus.[13-15] IL-41—also known as meteorin-like (Metrnl) protein—is a cytokine involved in various biological processes, including immune response modulation and tissue repair. Also referred to as IL-41 du e to its cytokine-like functions and, it is encoded by the METRNL gene, located on human chromosome 17 (17q25.3).[16] Although the specific cells responsible for producing IL-41, its target cells, and the signalling pathways involved in its activation are still under investigation, research indicates that many tissues express this cytokine, particularly the barrier tissues of the skin, intestines, and respiratory tract. Additionally, IL-41 has been associated with innate and adaptive immunity, as it is expressed in alternatively activated and M2-like macrophages.[17]

This article was accepted:
Corresponding Author: Professor Dr. Inas Khalifa AL Sharquie
Email: iksharquie@yahoo.com, inasksharquie@comed.uobaghdad.edu.iq

IL-41 is a novel immunomodulatory cytokine associated with inflammatory conditions such as psoriatic arthritis and is also an anti-inflammatory agent in other conditions.[18-20] Its potential role in spinal inflammation, particularly in AS, has yet to be fully understood. However, early studies suggest that IL-41 may modulate inflammatory responses in tissue repair and immune response, which are central to AS pathogenesis. Further research is required to establish a clearer link between IL-41 and spinal inflammation in AS patients, but the cytokine's dual role in inflammation may indicate its relevance in disease mechanisms. Furthermore, given the promising results of inhibiting some interleukins in inflammatory conditions, including AS, in-depth investigations into pro- and anti-inflammatory cytokines are of utmost importance.[6,21] Thus, evaluating IL-41's role in AS may not only contribute to understanding its pathogenesis but also pave the way for the development of practical diagnostic tools and potentially more effective treatments, underscoring the significance of our research.

One limitation of current biomarkers for AS is their need for more specificity and sensitivity in tracking disease progression. While human leukocyte antigen (HLA-B27) is helpful for diagnosis, it does not correlate with disease severity or treatment response. Additionally, general inflammatory markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are nonspecific and cannot accurately reflect the dynamic inflammatory processes characteristic of AS.

The present study therefore evaluates the novel potential of IL-41 as a biomarker for AS by measuring its levels in patients' serum. Additionally, the correlation between IL-41 levels and AS activity was assessed, and other patient characteristics were evaluated. To the best of our knowledge, this is the first study to investigate the role of IL-41 in AS, offering a fresh perspective and potential breakthrough in our understanding of this complex disease.

MATERIALS AND METHODS

This study enrolled 88 patients over the age of 18 diagnosed with AS based on the Assessment of Spondylarthritis International Society for Spondylarthritis (ASAS) classification criteria.[22] The patients were divided into two subgroups: inactive (n=44) and active (n=44). Additionally, 44 healthy individuals who matched the age and sex of the patients were included as a control group. The participants were recruited from the Rheumatology Unit at the Baghdad Teaching Hospital between November 2023 and January 2024. Exclusion criteria included: patients with overlapping inflammatory disorders, such as rheumatoid arthritis, psoriasis or inflammatory bowel disease; pregnant women; patients with comorbidities, such as malignancies; and refusal to participate. The study was approved by the Committee of Scientific Ethics from the College of Medicine, University of Baghdad (approval number: 0231).

For each patient, recorded baseline data included disease duration, body mass index (BMI), sex, age and ESR. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) were used to evaluate disease activity and functional impairment, respectively. In both cases, patients were categorised into two groups, with < 4.0 considered inactive and ≥ 4.0 considered active.[23-24] The full patient information page data and consent forms were completed under the direction of a rheumatologist. Disease-related laboratory parameters included CRP, HLA-B27 and rheumatoid factor (RF). Blood samples (5 mL) were collected from the patients and healthy controls using disposable plastic syringes. Each blood sample was collected in a gel separation tube and then subjected to centrifugation at 3000 rpm for 15 minutes. After centrifugation, the serum samples were frozen at -20°C. The enzyme-linked immunosorbent assay technique (ELISA) was used to measure serum IL-41 (Cloud-clone Corp Company (USA) with product code SER740Hu), CRP levels (Cloud-clone Corp Company (USA) with product code EH0099), HLA-B27 (Elabscience Company (USA) with product code E-EL-H0157) and RF (FineTest Company (USA) with product code EH4269). All manufacturers' instructions were strictly followed during the testing process. All samples were run in duplicate. A plate reader was used to measure the absorbance at 450 nm. The immunological testing was conducted at the International Centre for Research and Development.

Statistical analysis

Statistical analyses were performed using the SPSS Statistical package (Version 26; SPSS, IBM) and Microsoft Office Excel (2010) for drawing the figures, except for the receiver operating characteristic (ROC) curve. Normally distributed data are expressed as (Mean ± SD) (randomised sampling). Independent samples of students (t-tests), analyses of variation (ANOVA) tests and least significant difference (LSD) tests were performed to allow for comparisons of quantitative variables between studied groups (e.g., age, BMI, serum 41 ng/mL). Pearson and chi-square tests were used for comparisons of qualitative variables among the groups (i.e., age, BMI and smoking). Pearson's correlation tests were used to identify relationships among serum 41 ng/mL, age, BMI, duration of AS disease, ESR, CRP, HLA–B27, BASDI and BASFI disease activity. The validity of these tests was estimated with an ROC curve, cut-off value, area under curve (AUC), sensitivity (%), specificity (%), positive predictive value % (PPV), negative predictive value % (NPV) and accuracy. The statistical significance threshold (P–value) was set at P>0.05 for non-significant differences (NS), P<0.05 for significant difference (S) and P<0.01 for highly significant difference (HS).

RESULTS

Table I shows 88 patients with AS, between 18 and 59 years of age, were divided into two groups according to AS disease severity (44 inactive and 44 active). In addition, 44 healthy individuals whose ages ranged from 18 to 57 years old were used as control subjects. Non-significance was set at P>0.05. The greatest number of subjects was within the age range of 31–40 years for the controls (20, 45.5%) and AS patients (31, 35.2%). This was followed by the age range of 18–30 years, with 36.39% (16) controls and 29.5% (26) AS patients in this group. Next was the 41–50-year age range, with 11.4% (5) in controls and 28.46% (25) in AS patients (P = 0.174). The mean ages of the two studied groups were similar, with controls at 33.21 ± 9.113 years and AS patients at 36.47 ± 9.151 years (P = 0.038).

Table I: Demographics and other parameters: distributions within AS patient groups and controls

Parameters	Activity of AS disease			P-value	
	Control	Inactive	Active		
Age group					
18–30	16 (36.4%)	18 (40.9%)	8 (18.2%)	P = 0.107	
31–40	20 (45.5%)	12 (27.3%)	19 (43.2%)		
41–50	5 (11.4%)	11 (25%)	14 (31.8%)		
51–60	3 (6.8%)	3 (6.8%)	3 (6.8%)		
Sex Male	30 (68.2%)	37 (84.1%)	24 (54.5%)	P = 0.011	
Female	14 (31.8%)	7 (15.9%)	20 (45.5%)		
BMI group					
Normal weight	24 (54.5%)	4 (9.1%)	11 (25%)	P = 0.005	
Overweight	15 (34.1%)	15 (34.1%)	16 (36.4%)		
Obese	5 (11.4%)	25 (56.8%)	17 (38.6%)		
Smoking					
Smokers	17 (38.6%)	20 (45.5%)	13 (29.5%)	P = 0.811	
Non-smokers	27 (61.4%)	24 (54.5%)	31 (70.5%)		
Age					
Mean	33.21	34.49	38.11	A	P =0.249
Std. Deviation	9.113	10.317	7.973	B	P =0.004
Std. Error	1.35	1.562	1.195	C	P =0.072
ANOVA test (P-value):	**P = 0.017**				
BMI					
Mean	25.740	27.212	29.066	A	P =0.191
Std. Deviation	4.3702	5.534	5.573	B	P =0.003
Std. Error	0.650	0.833	0.840	C	P =0.102
ANOVA test (P-value):	**P = 0.021**				

Note: P>0.05 = non-significant difference, P<0.01 = highly significant difference.
A = control vs. inactive; B = control vs. active; C = inactive vs. active.

Table II: Mean distributions of parameters within AS patient groups

Parameter	Activity of AS	N	Mean	Std. Deviation	Std. Error	P-value	
Duration							
	Inactive	44	7.61	4.602	0.717	P = 0.838	
	Active	44	7.38	4.911	0.742		
	Total	88					
Disease activity							
BASDI	Inactive	44	2.413	1.083	0.163	P = 0.004	
	Active	44	5.112	0.973	0.147		
	Total	88					
BASFI	Inactive	44	2.523	1.222	0.185	P = 0.002	
	Active	44	5.267	1.283	0.194		
	Total	88					
ESR	Control	44	6.123	3.662	0.546	A	P = 0.002
	Inactive	44	15.104	10.507	1.583	B	P = 0.004
	Active	44	22.595	13.799	2.081	C	P = 0.006
	Total	132	ANOVA test (P–Value): P = 0.005				
CRP (mg/l)	Control	44	2.57	0.334	0.052	A	P = 0.003
	Inactive	44	2.38	0.375	0.057	B	P = 0.007
	Active	44	1.95	0.298	0.054	C	P = 0.001
	Total	132	ANOVA test (P–Value): P = 0.005				
RRF (IU/mL)	Control	44	27.99	5.315	0.811	A	P = 0.097
	Inactive	44	25.71	5.753	0.873	B	P = 0.236
	Active	44	26.12	7.216	1.101	C	P = 0.801
	Total	132	ANOVA test (P-Value): P = 0.471				
HLA-B27 ng/mL)	Control	44	4.604	1.060	0.162	A	P = 0.005
	Inactive	44	6.247	1.032	0.167	B	P = 0.002
	Active	44	9.545	2.358	0.354	C	P = 0.007
	Total	132	ANOVA test (P–Value): P = 0.003				

Note: P>0.05 = non-significant difference, P<0.01 = highly significant difference.
A = control vs. inactive, B = control vs. active; C = inactive vs. active.

Table III: Mean distributions of IL-41 levels within AS patient groups and controls

		IL-41 (ng/mL)				
Activity of AS	**N**	**Mean**	**Std. Deviation**	**Std. Error**	**P-value**	
Control	44	8.495	0.985	0.150	A	P = 0.002
Inactive	44	12.411	1.672	0.252	B	P = 0.004
Active	44	23.037	5.268	0.795	C	P = 0.001
Total	132	ANOVA test (P-Value):		P = 0.003		

Note: P>0.05 = non-significant difference, P<0.01 = highly significant difference.
A = control vs. inactive; B = control vs. active; C = inactive vs. active.

Table IV: Treatment intake distributions within AS patient groups

Type of Medication		**Activity**				**P-value**
		Inactive		**Active**		
		Intake	**NON**	**Intake**	**NON**	
Sulfasalazine	N	0	44	4	40	P = 0.041
	%	0%	100%	9.1%	90.9%	
Methotrexate	N	0	44	1	43	P = 0.315
	%	0%	100%	2.3%	97.7%	
Adalimumab (Humera)	N	0	44	1	43	P = 0.315
	%	0%	100%	2.3%	97.7%	
Etanercept (Enbrel)	N	31	13	30	14	P = 0.817
	%	70.5%	29.5%	68.2%	31.8%	
Adalimumab (Amgevita)	N	7	37	6	38	P = 0.764
	%	15.9%	84.1%	13.6%	86.4%	
Infliximab (ixifi)	N	3	41	0	44	P = 0.078
	%	6.8%	93.2%	0%	100%	
Infliximab (Remsima)	N	3	41	2	42	P = 0.645
	%	6.8%	93.2%	4.5%	95.5%	

Table V: Correlation study between IL-41 and HLA-B27 levels and other AS disease parameters

Pearson Correlation (patients with AS)		**IL-41 (ng/mL)**	**HLA-B27 (ng/mL)**
HLA-B27	r	0.702	
(ng/mL)	P-value	0.0001	
	Sign.	HS	
Age	r	0.146	0.239
	P-value	0.174	0.025
	Sign.	NS	Significant
BMI (kg/m2)	r	0.028	0.158
	P-value	0.794	0.141
	Sign.	NS	NS
Duration	r	0.163	0.002
	P-value	0.130	0.989
	Sign.	NS	NS
BASDI	r	0.633	0.545
(disease activity)	P-value	0.0004	0.0006
	Sign.	HS	HS
BASFI	r	0.591	0.578
(disease activity)	P-value	0.0001	0.0009
	Sign.	HS	HS
ESR mm/h	r	0.170	0.114
	P-value	0.112	0.291
	Sign.	NS	NS
CRP (ng/mL)	r	-.382	-.304
	P-value	0.0007	.004
	Sign.	HS	HS
RF (IU/mL)	r	.104	.140
	P-value	0.333	0.195
	Sign.	NS	NS

Note: P>0.05 = non-significant difference (NS), P<0.01 = highly significant difference (HS).

Male patients predominated, accounting for 64.8% (57) of patients with AS and 65.91% (29) of the control group (P = 0.896).

Regarding BMI, obesity was most common among AS patients, at 47.8% (42), followed by normal weight (35.2%, 31) and overweight (28.4%, 25). In contrast, in the controls, normal weight was at 50% (22), followed by overweight at 36.4% (16) and obese 13.6% (6) (P = 0.004).

Patients with AS were more likely to be non-smokers (65.9%, 58) than smokers (34.1%, 30), while the distribution was even in the control group, at 50% (22) for both smokers and non-smokers (P = 0.976).

The mean BMI in patients with AS was 28.1109 ± 5.58991, which was significantly higher than that of the control group, at 25.7402 ± 4.37015, (P = 0.019).

The 31–40-year age group was the largest among patients with active AS, at 43.2% (19), and controls, at 45.5% (20), whereas those with inactive AS were most likely to be in the 18–30-year age range (40.9%, 18) (P = 0.107).

Among patients with inactive AS, 84.1% (37) were males, and among controls, 30 (68.2%) were males. In contrast, among those with active AS, only 54.5% (24) were males and 45.5% (20) were females (P = 0.011 at P<0.05).

For BMI, obesity rates were elevated among patients with inactive AS (56.8%, 25) and among those with active AS (38.6%, 17); this was followed by overweight (active at 36.4% [16] and inactive at 34.1% [15]). Normal weight was the most common in the control group at 54.5% (24) (P = 0.005).

Regarding smoking, non-smokers made up the largest group both among patients with active AS 31 (70.5%) and among those with inactive AS 24 (54.5%), and their healthy control was highly frequent, while smokers made up 38.6% (17) of the control group, 45.5% (20) of the inactive AS group and 29.5% (13) of the active AS group (P = 0.811).

The mean age was similar in all three groups, with the control group at 33.21 ± 9.113, inactive patients with AS at 34.49 ± 10.317 and active AS patients at 38.11 ± 7.973, with all differences non-significant at P>0.05, except for the difference between controls and patients with active AS, with P = 0.0004.

Mean BMI was also similar among controls (25.740 ± 4.3702), patients with inactive AS (27.212 ± 5.534) and those with active AS (29.066 ± 5. 573), with a non-significant difference at P>0.05 – except for between controls and patients with active AS, where P = 0.003.

Table II shows a highly significant difference at P<0.01 for most parameters when comparing patients with different disease severity. The exceptions are RF IU/mL and duration, which show a non-significant difference at P>0.05 and similar mean ± standard deviations.

The mean for disease activity level was lower in patients with inactive AS (BASDI [2.413 ± 1.083] and BASFI [2.523 ± 1.222]) than in those with active AS (BASDI [5.112 ± 0.973] and BASFI [5.267 ± 1.283]).

The mean ESR mm/h result was higher in patients with active AS (22.595 ± 13.799) than in patients with inactive AS (15.104 ± 10.507) and even lower in the controls (6.123 ± 3.662).

The mean CRP in sera was highest in the controls (2.57 ± 0.334), followed by inactive AS (2.38 ± 0.375) and then active AS (1.95 ± 0.298).

The mean HLA–B27 (ng/mL) was lower in the controls (4.604 ± 1.060) than in the patients with active (9.545 ± 2.358) and inactive AS (6.247 ± 1.032).

The results show that the mean IL–41 ng/mL in the sera of patients with AS (17.721 ± 6.609) is more elevated than in the control group (8.495 ± 0.984), with a highly statistically significant difference (P = 0.009 at P<0.01). Additionally, as shown in Table III, all statistical tests found that the IL–41 ng/mL in the sera of patients with active AS (23.037 ± 5.268) was higher than in patients with inactive AS (12.411 ± 1.672) and controls (8.495 ± 0.984).

Clearly, Etanercept (enbrel) was predominant in patients with inactive AS, at 70.5% (31), and in patients with active AS, at 68.2% (30). This was followed by Adalimumab (Amgevita), at 15.9% (7) in inactive AS and 13.6% (6) in active AS, showing no significant difference (P = 0.158). In most comparisons of medication intake in patients with inactive and active AS, except for sulfasalazine, there was a significant difference at P<0.05. Table IV shows the frequencies for each.

There were no significant differences in IL–41 ng/mL and HLA-B27 among AS patients and those on different medications. Levels of serum IL–41 and other parameters had highly significant inverse (negative) relationships (P<0.01) with CRP (r = -0.382, P = 0.0007). There were highly significant positive relationships (P<0.01) with HLA-B27 (r = 0.702, P = 0.0001), BASDI disease activity (r = 0.633, P = 0.0004) and BASFI disease activity (r = 0.591, P = 0.0001). All other correlations were identified as weakly positive and were not significant (P>0.05). However, HLA-B27 levels and other parameters were significantly positively correlated (P<0.05) with age (r = 0.239, P = 0.025). In addition, there was a significant positive relationship (P<0.01) between BASDI disease activity (r = 0.545, P = 0.0006) and BASFI disease activity (r = 0.578, P = 0.0009). All other correlations were weakly positive and classified as non-significant (P>0.05).

Validity of tests

The results demonstrated that serum IL-41 can be used for diagnosing patients with AS at a cut-off value of 9.35 ng/mL and an AUC of 0.991. Moreover, the tests showed that sensitivity increased greatly (97.7%), with very good specificity (79.5%) and positive predictive (90.5%) and negative predictive (94.6%) values. The accuracy of the tests was also high (92.38%), with a highly statistically significant

difference (P<0.001). Moreover, serum HLA–B27 was shown to have high validity, with a cut-off value of 5.2 ng/mL, an AUC of 0.953, a sensitivity of 95.5%, good specificity (70.5%), and positive predictive and negative predictive values of 86.6% and 88.6%, respectively. In addition, its accuracy was 67.12%, and it had a highly statistically significant difference at P < 0.007.

DISCUSSION

IL-41 is gaining recognition within the immunological community for its roles in autoimmune pathophysiology. Its effects on both the pro-inflammatory[25] and anti-inflammatory pathways[26-27] suggest its utility as a biomarker for various inflammatory conditions. AS, a chronic condition affecting the axial skeleton, poses diagnostic challenges due to its complex symptoms and similarity to other rheumatologic diseases.[28] Here, we critically assess the findings of this study in light of the existing literature to explore IL-41's capability to refine diagnostic criteria and enhance AS-treatment strategies.

The results showed that IL-41 serum levels are significantly higher in patients with active AS, highlighting its potential as a biomarker for assessing disease activity. This correlation is particularly compelling because it dovetails with emerging research which suggests that cytokines play a central role in the pathogenesis and monitoring of inflammatory diseases.[29] In the context of AS, the activity of the disease is often evaluated through clinical assessments and inflammatory markers such as CRP and ESR. However, levels of these markers do not always correlate directly with symptoms or long-term outcomes, which complicates disease management.[30] The use of IL-41 as a biomarker may offer a more direct and reliable measurement of the underlying inflammation specific to AS pathophysiology. IL-41 levels may serve as a potential biomarker for disease activity in AS, but further multicentre studies with larger sample sizes are required to confirm its role and explore its potential clinical applications. Furthermore, studies on other rheumatologic diseases have shown that cytokines such as IL-6 and IL-23 are valuable for both diagnosis and therapeutic targets.[31] The hypothesis that IL-41 could serve a dual role in both diagnostic and therapeutic frameworks is supported by our finding that high IL-41 levels are directly correlated with disease severity in patients with AS.

The analysis of IL-41 levels in relation to demographic and clinical characteristics in patients with AS yields additional insights into the disease's heterogeneity and its biomarkers. This study delineated how factors such as age, sex, BMI, and specific clinical markers (e.g., HLA-B27 and CRP) correlate with variations in IL-41 serum levels. Sex and age are critical demographic factors that often influence disease expression and prognosis in autoimmune diseases.[32-33] While we did not assess changes in IL-41 levels with treatment, the study suggests that IL-41 levels are associated with disease activity in AS and may serve as a potential biomarker. However, its robustness across various clinical variables, including treatment, warrants further investigation in larger, longitudinal studies. This implies broad applicability for IL-41 in clinical settings, irrespective of patient age or sex. Conversely, there was a notable association between IL-41 levels and BMI, with higher BMI correlating with increased cytokine levels. This finding is consistent with the literature, suggesting that adipose tissue can influence systemic inflammation and cytokine production.[34] The finding also raises the possibility that IL-41 could be used to evaluate metabolic aspects of inflammation in AS, which are increasingly recognised as important in the disease's pathology.[35] Moreover, the findings regarding clinical characteristics such as HLA-B27—a genetic marker strongly associated with AS—reveal that higher IL-41 levels correlate significantly with the presence of HLA-B27.[36] This result underscores IL-41's potential to serve not only as a marker of disease activity but also as an indicator of underlying genetic predispositions that exacerbate the disease.

The correlation between IL-41 and CRP, a well-established marker of inflammation[37-38] and therapeutic target[39], was significant. This finding reinforces the use of IL-41 as a biomarker for inflammatory status in patients with AS. The integration of IL-41 with traditional markers like CRP could enhance the precision of disease monitoring and potentially guide therapeutic interventions more effectively. These demographic and clinical insights into IL-41 levels not only augment our understanding of its role in AS but also suggest a multifaceted utility in diagnosing and managing the disease.

The comparative analysis between patients with AS and healthy controls in the study provides crucial insights into the specificity and sensitivity of IL-41 as a biomarker. Significantly higher levels of IL-41 in patients with AS (particularly those with active disease) compared to healthy controls underscore its potential utility in distinguishing between diseased and non-diseased states. The control group's IL-41 levels were consistently lower across all demographic and clinical variables, which reinforces the biomarker's specificity for inflammatory processes specific to AS. This distinction is critical for clinical applications, particularly in differential diagnosis, where distinguishing AS from other inflammatory and non-inflammatory conditions can be challenging.

The higher levels of IL-41 in patients with AS suggest that it is not a generic marker of inflammation but rather IL-41 is closely linked to the pathophysiological processes underlying AS. Moreover, the study's use of a healthy control group established baseline levels of IL-41, an essential step for developing diagnostic criteria. Establishing such baselines is a step towards integrating IL-41 measurements into routine diagnostic protocols, potentially improving early detection and accurate diagnosis of AS. The marked difference in IL-41 levels between active and inactive disease states within patients with AS compared to controls indicates IL-41's potential role in disease monitoring and management. This evidence supports the proposition that IL-41 can be a valuable addition to the biomarker panel for AS, not only for diagnostic purposes but also for the stratification of disease severity and monitoring of treatment efficacy.

CONCLUSION

This study provides strong evidence that serum IL-41 is higher in patients with AS and correlates with disease activity. These findings suggest that IL-41 has significant potential as a

novel diagnostic biomarker for AS, offering a new avenue for more precise and effective management of this chronic inflammatory disease. To our knowledge, this study is the first to show the potential of IL-41 for AS diagnosis and monitoring.

CONFLICTS OF INTEREST

No conflicts of interest.

THE FUNDING STATEMENT

This research article is entirely funded by the authors.

REFERENCES

1. Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 2019; 7(22): 019-0057
2. Rosenzweig HL, Vance EE, Asare-Konadu K, Koney KV, Lee EJ, Deodhar AA, et al. Card9/neutrophil signalling axis promotes IL-17A-mediated ankylosing spondylitis. Ann Rheum Dis. 2024; 83(2): 214-22.
3. Jaber AS, Ad'hiah AH. A novel signature of interleukins 36α, 37, 38, 39 and 40 in ankylosing spondylitis. Cytokine 2023; 162: 156117.https://www.sciencedirect.com/science/article/pii/S1043466622003 26X
4. National Institute for Health and Care Excellence. National Institute for Health and Care Excellence. 2019. Diagnosis of ankylosing spondylitis. [Internet]. Accessed October 2023. Available at: https://cks.nice.org.uk/topics/ankylosing-spondylitis/diagnosis/.
5. Chisălău BA, Crînguș LI, Vreju FA, Pârvănescu CD, Firulescu SC, Dinescu Ș C, et al. New insights into IL-17/IL-23 signaling in ankylosing spondylitis (Review). Exp Ther Med 2020; 20(4): 3493-7
6. Yin Y, Wang M, Liu M, Zhou E, Ren T, Chang X, et al. Efficacy and safety of IL-17 inhibitors for the treatment of ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Res Ther 2020; 22(1): 020-02208
7. Sharquie IK. Biomarker significance of interleukins, IL-37 and IL-38 in patients with juvenile idiopathic arthritis. Medical Journal of Malaysia 2022; 7(4): 415-9.
8. Al Ghuraibawi ZAG, Sharquie IK, Gorial FI. A novel Link of Serum IL-39 Levels in Patients with Rheumatoid Arthritis. Iraqi Journal of Science 2023; 64(4): 1651-61.
9. Al Ghuraibawi ZA, Sharquie IK, Gorial FI. Diagnostic potential of interleukin-40 (IL-40) in rheumatoid arthritis patients. The Egyptian Rheumatologist 2022; 44(4): 377-80
10. Al Rubaye AM, Sharquie IK, Gorial FI. Novel Insights Into The Role Of Serum Interleukin-39 In Patients With Systemic Lupus Erythematosus. Iraqi Journal of Science.2024; 65(10): 5518-31. https://doi.org/10.24996/ijs.2024.65.10.17
11. Al-bassam WW, Al-Karaawi IA, Sharquie IK, Ad'hiah AH. Evaluation of interleukin-38 levels in serum of patients with coronavirus disease 2019. Journal of Medical Virology 2022; 94(8): 3642-52
12. Al Rubaye AM, Sharquie IK, Gorial FI. Serum interleukin 40: an innovative diagnostic biomarker for patients with systemic lupus erythematosus. The Medical journal of Malaysia. 2023;78(5):609-15.http://europepmc.org/abstract/MED/37775487
13. Rubaee AA, Faiq IC, Muhammad MALA, Sarmad MZ, Abeer MM. Diagnostic and Predictive Values of IL-6 in a Group of Iraqi Patients with Rheumatoid Arthritis IL-6 Journal of the Faculty of Medicine Baghdad 2023; 65(2): 116-21.
14. Abdualkader SN, Wahab Al-Shaikly A, Al-Mousawy KM, Al-Ezzi M, Hasso MG, Hassan ZE. Correlation between Interleukin-4 and Interleukin-6 and auto antibodies in Systemic Lupus Erythematosus. Journal of the Faculty of Medicine Baghdad. 2010;51(4):416-8.https://doi.org/10.32007/jfacmedbagdad.5141097
15. Al-Zubaidi NK, Al-Fakhar SA, Al-Osami MH. Correlation between Demographic Characteristic and Oxidized Low Density Lipoprotein (OxLDL-IgM and OxLDL-IgG) Antibodies levels in patients with Systemic Lupus Erythematosus Patients. Journal of the Faculty of Medicine Baghdad 2024; 66(2): 171-7. https://doi.org/10.32007/jfacmedbagdad.6612002
16. Zheng S-l, Li Z-y, Song J, Liu J-m, Miao C-y. Metrnl: a secreted protein with new emerging functions. Acta Pharmacologica Sinica. 2016;37(5):571-9.https://doi.org/10.1038/aps.2016.9
17. Ushach I, Burkhardt AM, Martinez C, Hevezi PA, Gerber PA, Buhren BA, et al. METEORIN-LIKE is a cytokine associated with barrier tissues and alternatively activated macrophages. Clinical Immunology. 2015; 156(2): 119-27. https://www.sciencedirect.com/science/article/pii/S1521661614002666
18. Bridgewood C, Russell T, Weedon H, Baboolal T, Watad A, Sharif K, et al. The novel cytokine Metrnl/IL-41 is elevated in Psoriatic Arthritis synovium and inducible from both entheseal and synovial fibroblasts. Clin Immunol 2019; 208(108253): 27.
19. Onuora S. Novel cytokine, IL-41, linked with PsA. Nat Rev Rheumatol 2019; 15(11): 019-0314
20. Gong L, Zhou Y, Shi S, Ying L, Li Y, Li M. Increased serum IL-41 is associated with disease activity in rheumatoid arthritis. Clinica Chimica Acta. 2023;538:169-74.https://www.sciencedirect.com/science/article/pii/S0009898122013882
21. Yan M, Fang X, Guo J, Yin W. Effectiveness of interleukin-17A inhibitors in patients with ankylosing spondylitis: A protocol for systematic review and meta-analysis. Medicine 2022; 101(49): 0000000000032224
22. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. Journal of Autoimmunity. 2014;48-49:128-33.https://www.sciencedirect.com/science/article/pii/S0896841114000183
23. Kwon OC, Park MC. BASDAI cut-off values corresponding to ASDAS cut-off values. Rheumatology 2022; 61(6): 2369-74
24. Ørnbjerg LM, Georgiadis S, Kvien TK, Michelsen B, Rasmussen S, Pavelka K, et al. Impact of patient characteristics on ASDAS disease activity state cut-offs in axial spondyloarthritis: results from nine European rheumatology registries. RMD Open 2024;10(4): 2024-004644
25. Gong L, Zhou Y, Shi S, Ying L, Li Y, Li M. Increased serum IL-41 is associated with disease activity in rheumatoid arthritis. Clin Chim Acta 2023; 538: 169-74
26. Cen T, Mai Y, Jin J, Huang M, Li M, Wang S, et al. Interleukin-41 diminishes cigarette smoke-induced lung inflammation in mice. Int Immunopharmacol. 2023; 124(Pt A): 21
27. Chen X, Chen X, Yang Y, Luo N, Yang J, Zhong L, et al. Protective role of the novel cytokine Metrnl/ interleukin-41 in host immunity defense during sepsis by promoting macrophage recruitment and modulating Treg/Th17 immune cell balance. Clin Immunol 2023; 254(109690): 7
28. Agrawal P, Tote S, Sapkale B. Diagnosis and Treatment of Ankylosing Spondylitis. Cureus. 2024;16(1)
29. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. Int J Mol Sci. 2019;20(23)
30. Spoorenberg A, van Tubergen A, Landewé R, Dougados M, van der Linden S, Mielants H, et al. Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. Rheumatology. 2005;44(6):789-95
31. Magyari L, Varszegi D, Kovesdi E, Sarlos P, Farago B, Javorhazy A, et al. Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications. World J Orthop. 2014;5(4):516-36
32. Lahita RG. Sex and gender influence on immunity and autoimmunity. Front Immunol. 2023;14(1142723)

33. Goronzy JJ, Weyand CM. Immune aging and autoimmunity. Cell Mol Life Sci. 2012;69(10):1615-23
34. Wang P, Mariman E, Renes J, Keijer J. The secretory function of adipocytes in the physiology of white adipose tissue. Journal of Cellular Physiology. 2008;216(1):3-13.https://onlinelibrary.wiley.com/doi/abs/10.1002/jcp.21386
35. Guo Y, Wei S, Yin M, Cao D, Li Y, Wen C, et al. Gas Chromatography-Mass Spectrometry Reveals Stage-Specific Metabolic Signatures of Ankylosing Spondylitis. Metabolites 2023; 13(10)
36. Braun J, Sieper J. Fifty years after the discovery of the association of HLA B27 with ankylosing spondylitis. RMD Open 2023; 9(3): 2023-003102.
37. Szalai AJ. C-reactive protein (CRP) and autoimmune disease: facts and conjectures. Clin Dev Immunol 2004; 11(3-4): 221-6.
38. Benhamou M, Gossec L, Dougados M. Clinical relevance of C-reactive protein in ankylosing spondylitis and evaluation of the NSAIDs/coxibs' treatment effect on C-reactive protein. Rheumatology. 2010; 49(3): 536-41.
39. Rizo-Téllez SA, Sekheri M, Filep JG. C-reactive protein: a target for therapy to reduce inflammation. Front Immunol. 2023; 14(1237729)

Ethical deliberations on video recording of patients in healthcare facilities– a scoping review

Hafizah Zainal Abidin, MEmMed[1], Hazdalila Yais Haji Razali, MMed2

[1]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia, [2]Department of Medical Ethics and Law, Universiti Teknologi MARA Malaysia, Sungai Buloh, Selangor, Malaysia.

ABSTRACT

Introduction: The modern healthcare landscape with the emergence of video recording, has found applications in research, training, audit, quality improvement, and safety surveillance. Notably, advancements in camera technology have led to the development of smaller, lighter devices, enabling discreet usage and enhancing usability in clinical settings. Its adoption represents more than technological advancement; it entails a complex balance between improving patient care and respecting individual rights. Ethical considerations surrounding patient privacy, ownership of recordings, patient autonomy and healthcare provider responsibilities have garnered significant attention. In Malaysia, the adoption of video recordings in clinical interactions and consultations has been accepted in research, training and several medical fields. However, recording patients during clinical practice can be challenging, as there are scarce ethical guidelines for its practice. This review aims to gather and categorise the ethical challenges associated with recording videos of patients in healthcare facilities globally and identify research gaps specific to Malaysian healthcare settings. By addressing the ethical challenges globally, we can ensure the responsible and ethical use of video recording technology to enhance patient care while respecting individual rights.

Materials and Methods: Articles from Scopus, Web of Science and PubMed databases were collected following PRISMA guidelines. Key term searches included "video recording," "ethical issues," and "patients." Inclusion criteria encompassed video and audio recording interactions between healthcare providers and patients in any clinical setting, final publications, and the English language. Exclusions were imaging or photography recording and non-clinical settings. The qualitative synthesis involved iterative reading, thematic coding analysis in Excel, and specific analysis to address the research question.

Results: Initial database search, identified 363 records. After screening, a total of 22 articles were included for analysis. Five themes were identified from the selected articles: i) privacy and confidentiality, ii) informed consent, iii) beneficence and non-maleficence, iv) integrity and professionalism and v) governance, policy and legal framework. Majority of the reviewed articles concentrate on backgrounds within the fields of psychiatry, neurology and surgical-based medical specialities. The identified themes have demonstrated consistency across the majority of the articles analysed. Among the most frequently discussed themes, it's evident that ethical concerns extend beyond just the patient's realm to encompass the responsibilities of the healthcare provider (HCP) as well. Both patients and HCPs have their respective rights and responsibilities in ensuring the ethical use of video recording in clinical settings.

Conclusion: In conclusion, this review has highlighted the multifaceted ethical challenges surrounding the integration of video recording in healthcare settings. While video recording offers benefits for patient care, education, and quality improvement, its adoption presents complexities. Ethical dilemmas concerning patient privacy, consent, and data management must be addressed alongside practical barriers like technological limitations and resource constraints. Collaboration among healthcare providers, policymakers, and stakeholders is crucial to navigating these challenges ethically. Future research should delve into patient perspectives, develop ethical guidelines, and assess the impact of video recording on patient outcomes. By understanding these implications, healthcare can effectively leverage video recording to improve patient care while maintaining ethical standards.

KEYWORDS:
Medical ethics; video recording; clinical medicine; legal liability; digital technology

INTRODUCTION

The contemporary healthcare landscape is witnessing a profound transformation with the integration of technology. The usage of video recording has proven to be a useful tool in many aspects. The usage of video recording has been established in several medical fields, mainly, in research,[1–3] training and teaching,[4–6] audit and quality improvements,[7,8] and safety surveillance.[9] It has also been used in various clinical contexts, such as geriatrics, neurology, neurosurgery, and niche fields like surgical endoscopy and sleep studies, to monitor symptoms, progression, and treatment effectiveness, becoming widespread with the advent of camera phones and formal consent since the late 2000s.

The integration of video technology has emerged as an indispensable tool in clinical settings. Its adoption in clinical interactions and consultations has been widely accepted. For

This article was accepted: 23 September 2024
Corresponding Author: Hafizah Zainal Abidin
Email: dr.hafizah@usim.edu.my

instance, video consultations conducted from ambulances to in-hospital physicians serve as a prime example, exemplifying how it elevates the quality of patient care.[10] Recent advancements and innovations in camera technology have resulted in smaller, lighter devices. This development has enabled individuals to wear cameras discreetly, marking a significant shift that enhances usability. The adoption of body-mounted cameras has demonstrated its ability to enhance transparency and precision among personnel during the delivery of medical care.[11] Research has also delved into enhancing time-sensitive healthcare documentation tasks leveraging video recording as a valuable tool.[12–14]

However, incorporating institution-installed cameras and body-mounted cameras represents more than just technological progress. It is a complex interplay between the imperative for enhanced patient care and the preservation of individual rights. The integration of video recording in healthcare settings brings forth a spectrum of ethical considerations that demand thoughtful examination. Notably, concerns surrounding the privacy of recorded materials and the rightful ownership of such recordings have been carefully deliberated.[15] The ethical debate surrounding patient autonomy and the necessity for informed consent, regardless of its applicability, has been a subject of extensive inquiry and analysis within the scholarly literature. The complexities of patient rights, including the balance between individual autonomy and the overarching responsibility of healthcare providers to ensure patient welfare have differing opinions. The decision-making process regarding informed consent for video recording is influenced by various factors, including the unique characteristics of the individual patient within a clinical setting and the intricate interplay of cultural, social, and legal dynamics at the local level.

Given the value-laden ethical issues in video recording during doctor-patient clinical interactions, we aim to gather and categorize the ethical challenges involved in recording videos of patients in healthcare facilities globally and to identify the potential research gaps in recording videos of patients in healthcare facilities that should be addressed in future studies. This review addresses two main questions: 1) What are the ethical challenges involved in recording videos of patients during clinical interactions in healthcare facilities worldwide? and 2) How do these ethical challenges apply to Malaysian medical practice?

MATERIALS AND METHODS

The articles are collected from Scopus, Web of Science and Pubmed databases dated 1 January 2014 to 31 Mac 2024. This study adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A key term search strategy was done using a combination of the following keywords: (i) videorecord* OR videotape OR (video AND record*) OR camera, (ii) ethical AND issue* OR ethical AND barrier* OR ethical AND challenge*, and (iii) patient*.

Articles were selected using inclusion criteria as follows: (i) video recording of interactions between healthcare providers and patients in any clinical setting, (ii) all final publication articles (iii) English language and (iv) worldwide. We excluded articles with (i) imaging or photography recording, and (ii) recording under the following circumstances: disaster, research, and non-clinical setting recording. The inclusion criteria (i) refer to the process of capturing and storing visual and audio footage of exchanges between healthcare providers and patients during clinical consultations or treatments within a healthcare facility. This practice aims to document the details of these interactions for purposes such as enhancing patient care, education, quality improvement, and legal documentation.

The first author conducted the initial database screening, which was subsequently reviewed and verified by the second author. Following the initial screening, both authors independently assessed the listed records for eligibility. Articles not related to the research questions were excluded, such as those involving recording as part of research methodology, disaster scenarios, simulated patient training, patients' own wearable cameras, home surveillance, staff surveillance, video calls, conferences, or consultations with patients at home. In the event of uncertainty about the reason for removal, a discussion is done until a consensus is reached between the authors. Microsoft Excel was used in this screening process.

Qualitative syntheses were then conducted. Full texts of the identified articles were iteratively read by authors. Excel spreadsheets are used for thematic coding analysis. First initial coding was done, following a second axial coding and similar codes were grouped into similar themes. The results of this review aim to answer the research question (1). These findings are then extrapolated to the context of Malaysian medical practice, addressing research question (2), and are presented in the discussion section.

RESULTS

Background on selected articles

From our initial database search, a total of 363 records are identified. Out of these, 126 were removed as they were ineligible and 45 were duplicates. A total of 192 records we screened according to the title and abstract obtained. A total of 157 articles were excluded due to being irrelevant to the research objectives, leaving 35 articles to be obtained. Further 13 articles were excluded due to unrelated to the research objectives. Examples of the reasons for exclusion are recording of research participants, recording during a disaster, recording of simulated patients, patients' own wearable/installed cameras, recording as surveillance at home, recording surveillance of staff, and video calls, video conferences or online consultation with the patient at home. A total of 22 articles were included for analysis in this review. Figure 1 shows the detailed search strategy process.

Eight original articles,[17–24] two systematic reviews,[25,26] five literature reviews,[9,27–30] four review articles,[31–34] one theoretical article,[35] one case series[36] and one case report[37] were analysed. The majority of the reviewed articles primarily concentrate on backgrounds within the fields of psychiatry, neurology and surgical-based medical specialities (refer to Table I).

Data Analysis

There are five themes identified from the selected articles: i) privacy and confidentiality, ii) informed consent, iii) beneficence and non-maleficence, iv) integrity and professionalism and v) governance, policy and legal framework.

Privacy and Confidentiality

One of the primary ethical concerns is the protection of patient privacy and confidentiality (refer to Table I). Being recorded and monitored can infringe on their personal space and autonomy,[17,18,37] especially if done without their knowledge.[25] Patients may not want their personal lives or medical conditions to be recorded without their permission. The location of the camera, whether situated in a public or private area, significantly influences the required level of privacy.[9]

The patient's specific situation also influences the necessary level of privacy. Patients expressed concerns about being recorded in their vulnerable moments which may have a potential impact on their recovery, dignity, and privacy.[19,27,36] For instance, during a surgical procedure, only the necessary view is recorded, while other areas are appropriately covered, as with draping.[31] Even in verbal interactions, such as sensitive doctor-patient conversations in psychiatry and psychotherapy, the content of the discussions remains confidential.[32,36]

Apart from addressing patients' privacy concerns, some papers delve into the privacy considerations of professional staff.[26,28,34,35] Protecting the privacy and confidentiality of healthcare providers (HCPs) involved in the recording is also important. Staff should have their privacy respected to the same level as patients, and considerations for their consent and comfort with being recorded should be addressed.

The use of technology inevitably raises additional concerns about privacy, particularly regarding potential data breaches or unauthorized access. Deidentification of recordings is a viable solution to safeguard patient privacy.[21,23,24,29,33] In specialities or areas where patient identification is unnecessary or individual identity is not a concern, it is essential to prioritize effective deidentification of patient recordings, especially when these recordings are intended for audit, quality improvement, and educational purposes. Furthermore, additional measures should be implemented when dealing with particularly vulnerable groups, such as mental health patients and paediatric populations, to ensure their privacy and security.[21–24]

Informed Consent

In adhering to patient autonomy, patients should be fully informed about the recording process. This includes the purpose of the recording, the type of video footage that will be captured, how it will be used, and who will have access to it. Obtaining informed consent from patients before recording any videos is essential to respect their autonomy and rights.[25–27,29,31–33,37] In countries where it is legally mandated, patients must be informed about how their data will be used, stored, and shared, ensuring that their privacy is protected in accordance with regulations such as the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA).[30]

Patients should be informed and given the opportunity to consent, or decline being recorded.[18,32,33] HCPs should be mindful of coercion during clinical treatment. Patients might feel pressured to agree to recording because of the authority of their HCPs. It's crucial for HCPs to recognize their influence and ensure that patients willingly consent to be recorded.[32,36]

When video recording involves patients with diminished capacity, such as the elderly, or those who never had capacity, such as paediatric or mental health patients, informed consent must be obtained from their parents, guardians, or proxies before any recording occurs. This process includes a clear explanation of the study's purpose, how the data will be used, and any potential risks involved.[21–24,30,37]

Obtaining patient consent for recording in emergency situations, such as resuscitation, is often impractical due to the urgency of the situation.[34,35] Lloyd et al.[35] suggest employing broad consent rather than informed consent, utilizing posted signage around the emergency department (ED) to inform all visitors that video footage recorded in the Resuscitation Rooms would be utilized for audit purposes.

Appenzeller et al. have outlined the consent requirements based on the areas being recorded.[9] While public spaces within healthcare facilities may not necessitate consent, consent is typically required for recording in private clinical spaces. The necessity of consent is closely tied to the purpose of the recording. For instance, in the case of video monitoring of patients in seclusion restraint rooms, where the benefits outweigh the risks, deferring consent may be considered acceptable.[9]

In some healthcare settings, recordings may involve third parties, such as family members, colleagues, or passersby, without their consent. Respecting the privacy and consent of all individuals involved in the recording process is crucial to prevent potential ethical issues.[25]

Apart from considering third parties from the patient's side, it's important to also think about third parties from the HCPs. Lloyd et al. introduced video recording as an audit tool in the Resuscitation Room, where both ED staff and clinicians from other specialities work.[35] These non-ED clinicians would also be recorded, so they should be informed about the new recording system. The authors note that the staff must feel this initiative is happening 'with them' rather than 'to them'. In certain facilities with legal requirements that mandate the activation of a body-worn camera, obtaining consent may be optional.[19] However, it is ethically justified on the necessity of adequately informing patients about their rights when such technology is utilized.

Beneficence and Non-Maleficence

In any event that there is a need to use video recording, it's essential to evaluate the balance between its benefits and potential harms before recording the patient, particularly in a patient with a complex medical background.[37] HCPs should

address concerns and discuss potential social implications with patients before implementing recording devices. Several benefits have been found in the usage of video recording in clinical medicine. Benefits include training and teaching,[27,31] audit and quality improvements,[34,35] safety surveillance[9,17,36] and medical documentation.[28] Funkenstein et al. stated that a unique characteristic of video recording is that it allows for greater clarity of subtle facial expressions, gestures, and interactions for healthcare providers.[36]

Erba et al., emphasize that relying solely on video recordings for clinical assessments can lead to misdiagnosis, thereby risking patient safety, and highlight the importance of recognizing the limitations of video evidence. Furthermore, it notes that poor video quality can adversely affect the diagnostic process, raising ethical concerns about the reliability of such assessments.[21]

Wiegandt et al. introduce the use of the Time-of-Flight camera, designed to avoid physical contact with neonates and emphasise that this approach is beneficial as it provides effective monitoring while minimising harm to vulnerable populations, such as preterm infants.[24]

Nevertheless, there are inherent risks involved in adopting video recording. The use of video as surveillance has been shown to risk mental well-being such as it may worsen patients' fear, distrust and delusion.[9,19] On the contrary, the article by Szabó et al. argues that the presence of cameras and the knowledge that seizures are being recorded may affect a patient's comfort and willingness to participate in the study, potentially impacting their mental health.[23]

When it comes to body-mounted cameras, they may present unique risks. Despite their small and inconspicuous nature, they must still function ethically as a healthcare tool. Utilizing them covertly may not be the optimal solution, as transparency is paramount. Staff who wear them have been observed to discourage patient engagement and impede the development of therapeutic relationships.[18] It may shift the focus away from care and further position staff and patients as oppositional parties that cannot trust each other On the other hand, when patients wear them, patients might experience social stigma or discomfort.[25]

In the use of video recording for any purpose, HCPs must balance the potential benefits with the risks to patients' physical, emotional, and psychological well-being.[31] The risk must be carefully considered and minimized. A recording may benefit one party (for example staff for audit and learning of resuscitation from the video) while adding risks for others (the patient that was involved in the resuscitation).[33]

Establishing clear and transparent patient selection criteria helps ensure that recording practices are conducted ethically and with consideration for patients' well-being and rights.[36] It also enables healthcare facilities to effectively manage risks and optimize the benefits of recording for various purposes. However, as all these are still at an early stage of implementation, more research is needed to ascertain the effectiveness of the recording process.[9,17] Continuous feedback is essential for providing constructive evaluations and facilitating improvements in video recording practices.[34]

Integrity and Professionalism

The transparency of video recording may affect not only patients but also HCPs. Surveillance can detect abuse of professional responsibility and regulate staff behaviour.[17] Staff should be able to voice out their concerns before recording system implementation.[35] A safe environment needs to be built so that the system can be trusted by not only patients but HCPs too.[19,35]

The acceptance of video recording will begin with the acceptance of the staff before it can be embraced by patients. As Funkenstein et al. mentioned, by showing patients that the therapist is willing to be scrutinized and vulnerable in front of the camera, therapists set a positive example for their videotaped patients about accepting and addressing their own inevitable vulnerabilities.[36]

Video recording allows for objective documentation of signs, such as a seizure episode, which facilitates multidisciplinary management by easing the importance of collaborative assessments between physicians and psychiatrists. Ethical practice in such contexts necessitates clear communication and shared decision-making among the healthcare team to ensure that the patient's best interests are prioritised.[22,25,28]

Responsible data management is a foremost important discussion in applying video recording. Patients should have control over the data recorded.[25,28] Storing recorded data has its benefits and risks. The potential benefit of stored video in future clarification and mitigating conflict may be a reason for it to be stored for documentation. A recording must receive the same care and protection as any other type of medical record.[28]

Storing personally identifiable video recordings of vulnerable patients demands a robust security system and meticulous attention to significant data protection issues.[9,18,19,26,27,32] Measures such as encryption, password protection, and physical security of storage devices should be implemented to safeguard patient information.[29] The use of data has to be done responsibly, and the recording must be done for legitimate purposes and not for personal gain or entertainment.[31,33,34]

Despite its apparent simplicity, video recording still necessitates a certain level of training. The inconsistent and inadequate training for staff was identified as a significant barrier to the effective utilisation of video recording technology.[18] Erba et.al., outline that trained epileptologists can make more accurate diagnoses from video alone compared to untrained individuals.[21] This highlights the ethical responsibility to ensure that only qualified professionals interpret video data to avoid misdiagnosis and ensure patient safety.

Despite the critical need for training to ensure adherence to policies, many staff members received minimal or no training, contributing to challenges in implementing and integrating video recording into clinical practice.

Table I: The list of articles included in this review

	First Author (Year)	Medical speciality	Article type	Brief description	Theme				
					Privacy and Confidentiality	Informed Consent	Beneficence and Non-Maleficence	Integrity and Professionalism	Governance, Policies and Legal Framework
1.	Allé M.C (2017) [25]	Neuro-psychology	Systemic review	An overview of the new therapeutic and research possibilities offered by wearable cameras.	√	√	√	√	
2.	Appenzeller Y.E (2020) [9]	Psychiatry	Literature review	A narrative review of the literature on video surveillance in psychiatry.	√	√	√	√	
3.	Berridge C. (2019) [17]	Geriatric/ Nursing	Original research	Anonymous online survey addressing the ethical challenges of web-connected cameras in the ageing population care workforce.	√		√	√	
4.	Cumpanas A.A. (2017) [27]	Urology	Review article	A discussion of ethical and legal issues related to live surgery.	√	√	√	√	
5.	Douglas S.L. (2021) [28]	Emergency Medicine	Review article	Video and audio recordings of patients in an Emergency Department	√	√	√	√	
6.	Dumestre, D.O. (2020) [29]	Plastic Surgery	Original article	Evaluation of smartphone application for clinical photograph and communication.	√	√	√	√	√
7.	Erba, G. (2016) [31]	Neurology	Original article	Predicted diagnosis of video-recorded epileptic patients.	√	√	√	√	
8.	Foye U (2024) [16]	Psychiatry	Original research	Semi-structured interviews with patients and staff to explore their perspectives on the practical and ethical issues related to the implementation of body-worn cameras.	√	√		√	
9.	Funkenstein A.B. (2014) [30]	Psychiatry	Case series	Examined two cases in which residents sought their patients' permission to videotape a session to explore the ethical issues unique to providing informed consent.	√	√	√	√	
10.	Gabrielli M. (2021) [17]	General surgery	Literature review	Ethical and legal understanding of video recording in the operating room.	√	√	√	√	
11.	Krecichwost, M. (2022) [32]	Speech therapy	Original article	Developing a speaker model to view and analyse speech abnormalities in patients.	√	√	√		
12.	Lloyd A. (2017) [33]	Emergency Medicine	Theoretical article	A practical guide for clinical services to navigate the challenges of embedding live video recording in an emergency department resuscitation room.	√	√	√	√	√
13.	Quach W.T. (2023) [26]	General Surgery	Systemic review	Ethical and legal analysis of the integration of high-resolution video in the operating room.	√	√		√	
14.	Rajwani K. (2023) [37]	Psychiatry	Review article	Investigate the ethical issues related to video recording of psychedelic therapy sessions.	√	√	√	√	
15.	Simma B (2021) [33]	Obstetrics	Review article	Discussing the ethical and medico-legal issues of the current state of delivery room video recording affecting long-term team performance or clinical outcomes.	√	√	√	√	√
16.	Szabó, CA. (2015) [22]	Neurology	Original article	Video recording of patient and EEC monitoring in seizure detection.	√	√	√	√	
17.	Tamune, H. (2024) [43]	Neurology	Case report	Catatonia diagnosis supported by EEG and video documentation assists in excluding other differential diagnosis	√	√	√	√	
18.	Thia B.C. (2019) [34]	Ophthalmology	Literature review	Current applications, methods, ethical and legal issues of video recording in ophthalmic surgery.	√	√		√	√
19.	Turnbull A.M.J. (2014) [35]	Ophthalmology	Literature review	Ethical and legal considerations with video documentation from routine surgical recording of ophthalmic surgery.	√	√	√	√	√
20.	van Dalen, ASHM. (2019)	Surgery	Literature review	A review of legal medical practice on the implementation of video and data recorder in the operation theatre.	√	√	√	√	√
21.	Wiegandt, FC. (2021) [24]	Pediatrics	Original article	Recording of neonates' abdominal movements in monitoring their breathing patterns.	√	√	√		
22.	Wilson K. (2023) [19]	Psychiatry	Original research	Exploratory online and in-person semi-structured interviews of patients, mental health staff and senior management on their perspectives on body-worn cameras.	√	√	√	√	

Governance, Policy, and Legal Frameworks

Incorporating recordings into medical records can serve as a valuable tool for comprehensive 'gold standard' medical documentation.[29] Maintaining recordings as part of medical records necessitates long-term storage. For legal purposes, recordings cannot remain de-identified or may require re-identification if initially de-identified. Transparency in recordings can have significant medico-legal implications. For instance, during a treatment or a procedure, complications or errors may be observed by patients or other involved parties.[29,33]

One of the steps in the practical guideline for live video recording for resuscitation audit in ED is to seek opinions, advice and written permission from the local Guardian and Data Protection Officer, the research ethics service and the legal office.[35] These inputs will assist to develop and share the working framework and guidelines. Consultations with legal advisors will assist in maintaining admissible recordings that may be useful in courts. The admissibility of recordings as evidence in court proceedings varies by consent process, ethics approval and local setting.[29,33]

Video recordings provide objective evidence, which is more accurate and reliable than testimonies. These recordings may be used by either the defence (doctor) or the plaintiff (patient) in legal proceedings. Previous legal cases have shown that video recording can potentially prevent medical litigation by accurately documenting procedures.[28]

DISCUSSION

All 22 articles included in this literature review were individually appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, which are widely recognized for their comprehensive and systematic approach to evaluating research quality and rigour. The JBI tools were selected because they provide specific criteria for assessing different

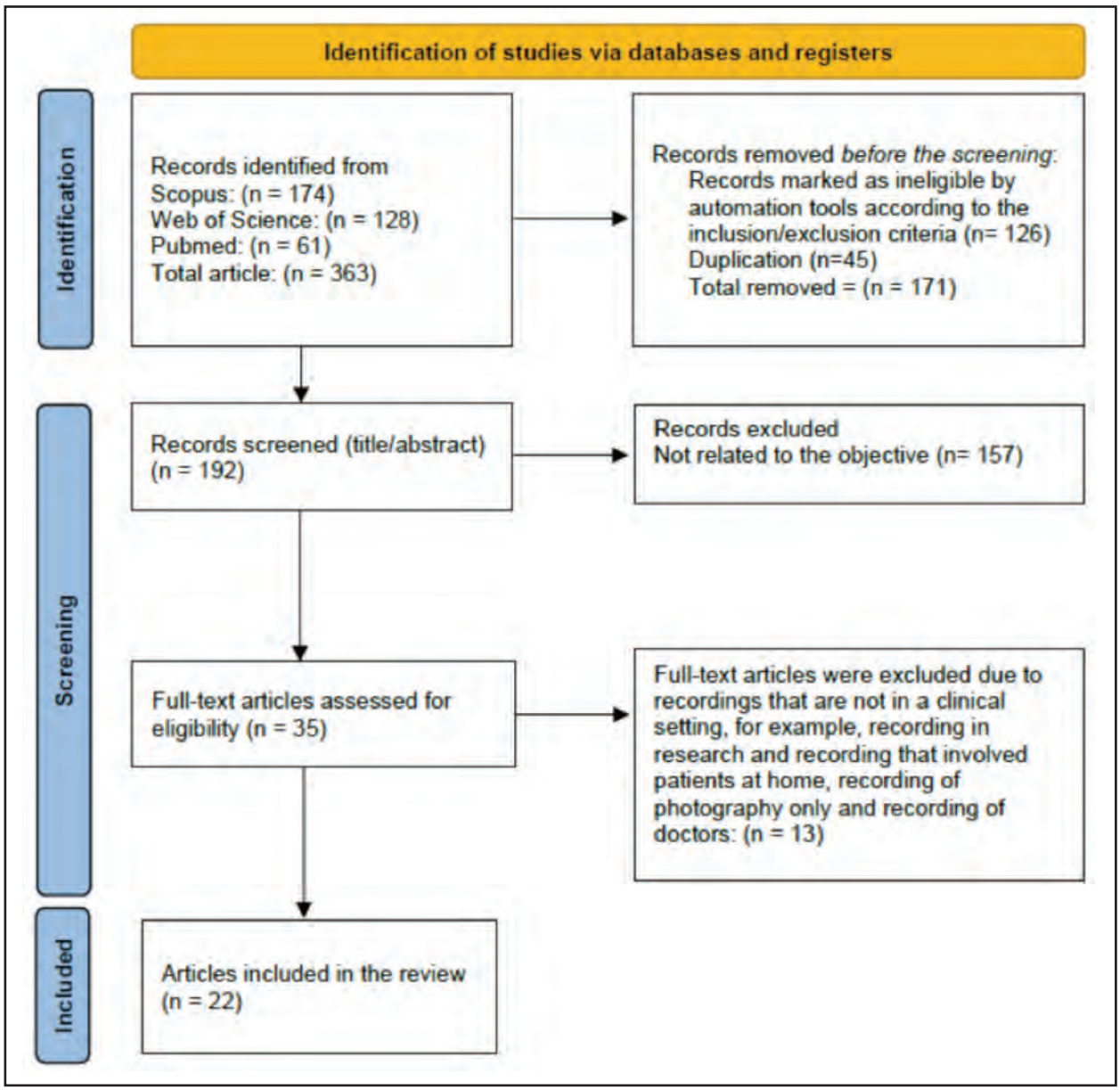

Fig. 1: Search strategy process of the study

study designs, ensuring a thorough evaluation of the methodological quality, validity, and reliability of each study. Upon appraisal, it is evident that the articles demonstrate a consistent commitment to addressing ethical considerations and methodological rigour. They cover a wide range of topics, from the importance of video recording to exploring methods for documenting the doctor-patient relationship.

The literature included in the review has clearly stated aims and the qualitative methodologies employed are appropriate for addressing the research questions. The findings are articulated and aligned with the research aims, supported by robust discussions. The articles also acknowledge their limitations, particularly concerning patient vulnerability and the potential impact of videotaping on the therapeutic relationship. Overall, the conclusions drawn are well-supported by the findings, emphasizing the need for transparency, individualized consent processes, and ongoing ethical considerations in the use of technology in healthcare settings.

The reviewed articles reveal that while video recording finds primary application in fields like psychiatry, neurology, emergency departments, and surgical specialities, its utility extends beyond these realms as well. These sectors have extensively documented the utility of video recording, illustrating its pivotal role in enriching patient care and medical training. For instance, in psychiatry, it serves as a vital medium for capturing patient interactions, behaviours, and treatment responses, aiding in precise diagnosis and treatment planning. Likewise, within emergency departments, it facilitates the documentation of critical procedures, patient assessments, and multidisciplinary team

communication, ultimately contributing to better clinical outcomes and care quality.

This multifaceted tool not only elevates patient care but also revolutionizes medical education and training in surgical specialities. By recording and reviewing procedures and surgical techniques, it enhances the learning journey for medical students, residents, and practitioners alike. Integrating video recording into the documentation of a surgical procedure empowers healthcare providers to offer comprehensive descriptions of patient care practices.

This review has shed light on the widespread ethical dilemmas associated with the adoption of video recording across various contexts. The identified themes have demonstrated consistency across the majority of the articles analysed. Interestingly, among the most frequently discussed topics, including patient privacy, confidentiality, and the integrity of data management, it's evident that ethical concerns extend beyond just the patient's realm to encompass the responsibilities of HCPs as well. Both patients and HCPs have their respective rights and responsibilities in ensuring the ethical use of video recording in clinical settings. In Malaysia, according to the Audio and Visual Recordings Guideline 003/2023, the Malaysian Medical Council (MMC) clarifies that recordings integrated into a patient's medical records as part of their care or treatment do not necessitate separate consent if the patient has already consented to the care or treatment inclusive of such recordings.[38] However, these recordings, if utilized for educational, training, or research purposes, can be employed without additional consent only if the patient had previously consented as part of their care, and provided the recordings are anonymized by removing any identifying patient information beforehand. Interestingly, paragraph 19 of the same guideline introduces a caveat: practitioners are encouraged to inform patients about any secondary uses of recordings when seeking consent, documenting such discussions in the patient's medical records.

Similarly, the guideline for Making and Using Visual and Audio Recordings of Patients by the British Medical Council (BMC) reflects analogous principles.[39] While certain recordings, like routine clinical investigations, are implicit in the consent for treatment, practitioners are advised to inform patients about the potential secondary uses of recordings during consent discussions, especially if they involve certain procedures listed in the guidelines. Additionally, any disclosures or uses of recordings for secondary purposes must ensure prior anonymization to safeguard patient confidentiality, in alignment with regulations and guidance from relevant authorities.

BMC emphasizes the necessity of patient consent before disclosing identifiable recordings, except in cases mandated by law or deemed to be in the public interest. Anonymized or coded recordings may be disclosed for research, teaching, or healthcare-related purposes without consent, although practitioners must exercise caution to ensure complete anonymization to safeguard patient privacy, especially before publication. Conversely, the MMC adopts a stricter stance. It addresses situations where practitioners possess recordings predating the guideline issuance, stressing the importance of anonymization if consent records are absent. MMC outlines detailed procedures for recording unexpected events, emphasizing the necessity of seeking patient consent whenever possible and promptly informing unconscious or sedated patients upon recovery. The MMC mandates that recordings must be used solely for the specified purpose agreed upon with the patient and should be erased or destroyed promptly if consent is withheld or withdrawn. This review highlights the significance of confidentiality and privacy as recurring ethical issues, yet we also want to underscore the potential variance in legal guidance across continents. Therefore, it's imperative for practitioners to thoroughly grasp the local guidelines governing video recording practices.

Looking forward, the fast-emerging technologies and innovations related to video recording systems, such as wearable cameras, telemedicine platforms, and artificial intelligence-driven analytics, have vast potential for healthcare delivery. HCPs and stakeholders must not only understand the ethical challenges but also the technical aspects of video recording to effectively manage the recording process. This preparation involves not only ensuring the availability of suitable equipment but also adhering to ethical practices outlined in local policies.

LIMITATIONS

This review has several limitations. Firstly, the majority of the literature focuses on the perspectives of HCPs, with limited studies exploring patients' views on video recording. Additionally, this paper does not analyze the topic related to patients who are recording interactions with their doctors. This aspect of the discussion may present both similarities and differences in practical and ethical considerations compared to recordings made by HCPs.

In many current clinical settings, the adoption of video recording is still in its early stages. As a result, the analysis presented may not encompass all potential ethical considerations and practical challenges associated with video recording in healthcare settings. The ethical challenges stemming from technological limitations, resource constraints, and logistical considerations have not been thoroughly examined in this analysis.

Ultimately, there may exist inherent biases in both the selection of literature and the interpretation of findings, potentially influencing the objectivity of the review. Authors might not possess in-depth familiarity with the clinical settings discussed in the articles, which could further impact the impartiality of the analysis. The review also may be influenced by the availability of published literature, potentially overlooking unpublished studies or grey literature.

CONCLUSION

In conclusion, this review has shed light on the multifaceted ethical challenges surrounding the implementation of video recording in healthcare settings. While video recording holds

promise as a valuable tool for enhancing patient care, education, and quality improvement initiatives, its adoption is not without complexities. Ethical dilemmas related to patient privacy, consent, and data management must be carefully navigated, alongside practical barriers such as technological limitations, resource constraints, and logistical considerations. It is imperative for HCPs, policymakers, and stakeholders to engage in ongoing dialogue and collaboration to address these challenges and ensure that the implementation of video recording in healthcare is conducted ethically, responsibly, and in a manner that prioritizes patient welfare.

In light of the insights gained from this review, future research endeavours should aim to delve deeper into the nuances of video recording in healthcare, including the exploration of patient perspectives, the development of robust ethical guidelines and regulatory frameworks, and the evaluation of the impact of video recording on patient outcomes and healthcare delivery. By fostering a comprehensive understanding of the ethical, practical, and clinical implications of video recording, the healthcare community can harness the potential of this technology to improve patient care while upholding the highest standards of ethical conduct and professionalism.

ACKNOWLEDGEMENTS

This work was supported by Universiti Sains Islam Malaysia with grant code PPPI/FPSK/0122/USIM/13822 dated 1st March 2022.

REFERENCES

1. Dewolf P, Rutten B, Wauters L, Van den Bempt S, Uten T, Van Kerkhoven J, et al. Impact of video-recording on patient outcome and data collection in out-of-hospital cardiac arrests. Resuscitation 2021; 165: 1–7.
2. Golembiewski EH, Espinoza Suarez NR, Maraboto Escarria AP, Yang AX, Kunneman M, Hassett LC, et al. Video-based observation research: A systematic review of studies in outpatient health care settings. Patient Educ Couns 2023; 106: 42–67.
3. Todd AL, Roberts L, Foster K. Feasibility of video recording interpersonal interactions between patients and hospital staff during usual care. Pilot Feasibility Stud 2022; 8: 1–9.
4. Dohms MC, Collares CF, Tibério IC. Video-based feedback using real consultations for a formative assessment in communication skills. BMC Med Educ 2020; 20: 1–9.
5. Fein DG, Eisen LA. Video Body Cameras Bridge the Gap Between Simulation and Patient Care During Emergency Airway Management. Chest 2020; 158: 24–25.
6. Holm-Hansen CC, Poulsen A, Skytte TB, Stensgaard CN, Bech CM, Lopes MN, et al. Video recording as an objective assessment tool of health worker performance in neonatal resuscitation at a district hospital in Pemba, Tanzania: A feasibility study. BMJ Open; 12. 2022.
7. Dewar A, Lowe D, Mcphail D, Clegg G. The use of body-worn cameras in pre-hospital resuscitation. Br Paramed J 2019; 4: 4.
8. Wong JZW, Park PSW, Frost T, Stephens K, Newk-Fon Hey Tow FK, Garcia PG, Senanayake C, et al. Using body cameras to quantify the duration of a Code Stroke and identify workflow issues: A continuous observation workflow time study. BMJ Open; 13. 2023.
9. Appenzeller YE, Appelbaum PS, Trachsel M. Ethical and practical issues in video surveillance of psychiatric units. Psychiatr Serv 2020; 71: 480–486.
10. Vicente V, Johansson A, Selling M, Johansson J, Möller S, Todorova L. Experience of using video support by prehospital emergency care physician in ambulance care - an interview study with prehospital emergency nurses in Sweden. BMC Emerg Med 2021; 21: 1–9.
11. Ho JD, Dawes DM, McKay EM, Taliercio JJ, White SD, Woodbury BJ, et al. Effect of an EMS body-worn camera. BMJ Open 2019; 9: A3.1-A3.
12. Ho JD, Dawes DM, McKay EM, Taliercio JJ, White SD, Woodbury BJ, et al. Effect of Body-Worn Cameras on EMS Documentation Accuracy: A Pilot Study. Prehospital Emerg Care 2017; 21: 263–71.
13. Denecke, K., Meier, L., Bauer, J. G., Bender, M., & Lueg, C. Information Capturing in Pre-Hospital Emergency Medical Settings (EMS). Stud Health Technol Inform 2020; 270: 613–617.
14. Iserson KV, Allan NG, Geiderman JM, Goett RR. Audiovisual recording in the emergency department: Ethical and legal issues. Am J Emerg Med 2019; 37: 2248–52.
15. Shah NA, Jue J, MacKey TK. Surgical Data Recording Technology: A Solution to Address Medical Errors? Ann Surg 2020; 271: 431–3.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71.
17. Berridge C, Halpern J, Levy K. Cameras on beds: The ethics of surveillance in nursing home rooms. AJOB Empir Bioeth 2019; 10: 55–62.
18. Foye U, Regan C, Wilson K, Ali R, Chadwick M, Thomas E, et al. Implementation of Body Worn Camera: Practical and Ethical Considerations. Issues Ment Health Nurs 2024; 1–12.
19. Wilson K, Foye U, Thomas E, Chadwick M, Dodhia S, Allen-Lynn J, et al. Exploring the use of body-worn cameras in acute mental health wards: A qualitative interview study with mental health patients and staff. Int J Nurs Stud 2023; 140: 104456.
20. Dumestre DO, Fraulin F. Avoiding breach of patient confidentiality: trial of a smartphone application that enables secure clinical photography and communication. Plast Surg 2020; 28: 12–8.
21. Erba G, Giussani G, Juersivich A, Magaudda A, Chiesa V, Laganà A, et al. The semiology of psychogenic nonepileptic seizures revisited: Can video alone predict the diagnosis? Preliminary data from a prospective feasibility study. Epilepsia 2016; 57: 777–85.
22. Krecichwost M, Sage A, Miodonska Z, Badura P. 4D Multimodal Speaker Model for Remote Speech Diagnosis. IEEE Access 2022; 4: 1-17.
23. Szabó CÁ, Morgan LC, Karkar KM, Leary LD, Lie OV, Girouard M, et al. Electromyography-based seizure detector: Preliminary results comparing a generalized tonic-clonic seizure detection algorithm to video-EEG recordings. Epilepsia 2015; 56: 1432–1437.
24. Wiegandt FC, Biegger D, Fast JF, Matusiak G, Mazela J, Ortmaier T, et al. Detection of breathing movements of preterm neonates by recording their abdominal movements with a time-of-flight camera. Pharmaceutics2021; 13(5):721
25. Allé MC, Manning L, Potheegadoo J, Coutelle R, Danion JM, Berna F. Wearable Cameras Are Useful Tools to Investigate and Remediate Autobiographical Memory Impairment: A Systematic PRISMA Review. Neuropsychol Rev 2017; 27: 81–99.
26. Quach WT, Vittetoe KL, Langerman A. Ethical and Legal Considerations for Recording in the Operating Room: A Systematic Review. J Surg Res 2023; 288: 118–33.
27. Gabrielli M, Valera L, Barrientos M. Audio and panoramic video recording in the operating room: Legal and ethical perspectives. J Med Ethics 2021; 47: 798–802.
28. Turnbull AMJ, Emsley ES. Video recording of ophthalmic surgery-ethical and legal considerations. Surv Ophthalmol 2014; 59: 553–8.
29. Thia BC, Wong NJ, Sheth SJ. Video recording in ophthalmic surgery. Surv Ophthalmol 2019; 64: 570–8.

30. van Dalen AS, Legemaate J, Schlack WS, Legemate DA, Schijven MP. Legal Perspectives on black box recording devices in the operating environment. J Br Surg 2019; 106: 1433–41.
31. Cumpanas A, Ferician OC, Latcu SC, Pricop C, Bardan RT. Ethical, legal and clinical aspects of live surgery in urology - Contemporary issues and a glimpse of the future. Videosurgery Miniiv 2017; 12 (1): 1–6.
32. Rajwani K. The "Third" Eye: Ethics of Video Recording in the Context of Psychedelic-Assisted Therapy. Can J Bioeth 2023; 6: 8–15.
33. Simma B, den Boer M, Nakstad B, Küster H, Herrick HM, Rüdiger M, et al. Video recording in the delivery room: current status, implications and implementation. Pediatr Res.2024; 96(3): 610-5.
34. Douglas SL, McRae A, Calder L, de Wit M, Sivilotti ML, Howes D, et al. Ethical, legal and administrative implications of the use of video and audio recording in an emergency department in Ontario, Canada. BMJ Innov 2021; 7: 224–30.
35. Lloyd A, Dewar A, Edgar S, Caesar D, Gowens P, Clegg G. How to implement live video recording in the clinical environment: A practical guide for clinical services. Int J Clin Pract 2017; 71: e12951.
36. Funkenstein AB, Kessler KA, Schen CR. Learning through the lens: Ethical considerations in videotaping psychotherapy. Harv Rev Psychiatry 2014; 22: 316–22.
37. Tamune H, Tsukioka Y, Sakuma S, Taira D, Takaoka Y, Tamura N, et al. EEG and video documentation of benzodiazepine challenge in catatonic stupor: A case report. Neuropsychopharmacol Reports 2024; 44: 468–73.
38. Malaysian Medical Council. Audio and Visual Recordings Guideline of the Malaysian Medical Council 003/2023.[cited Dec 2023]. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://mmc.gov.my/wp-content/uploads/2024/01/Audio-and-Visual-Recordings.pdf&ved=2ahUKEwiQ1P_drcGIAxW1RmwGHXM5O6wQFnoECBIQAQ&usg=AOvVaw2BCe-6CJmYbwZCKLjTrn61
39. General Medical Council, United Kingdom. Making and using visual and audio recordings of patients. [cited Jan 2024] Available from: www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/making-and-using-visual-and-audio-recordings-of-patients.

SHORT COMMUNICATION

Quality control of Actinium-225 radiopharmaceuticals: Current challenges and solutions in Malaysia

Zarif Ashhar, BPharm(Hons)[1], Muhammad Fakhrurazi Ahmad Fadzil, BPharm(Hons)[2], Mohamad Aminudin bin Said, PhD[3], Abdullah Mujahid Muhammad, BPharm(Hons)[1], Subapriya Suppiah, MMed (Rad) (UM), FANMB[4]

[1]Nuclear Medicine Department, Sabah Women and Children Hospital, Locked Bag No. 187, Kota Kinabalu, Sabah, Malaysia, [2]Pharmacy Department, Institut Kanser Negara, Putrajaya, Malaysia, [3]Nuclear Medicine Department, Institut Kanser Negara, Putrajaya, Malaysia, [4]Pusat Pengimejan Diagnostik Nuklear, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

ABSTRACT

Development of Prostate Specific Membrane Antigen (PSMA)-targeted radiopharmaceuticals for theranostics has changed the treatment landscape for patients with metastatic castration-resistant prostate cancer (mCRPC). The emerging use of [^{225}Ac]Ac-PSMA-RLT has been effective and safe for the treatment of mCRPC. Nevertheless, challenges with the nuclear recoil of [^{225}Ac]Actinium radionuclides, which may release the daughter radionuclide from the radiopharmaceutical and lead to unnecessary irradiation of other organs, poses threats such as organ dysfunction. Therefore, this short communication aims to highlight the current situation in Malaysia and explain the solutions by using a risk-based approach analysis for the in-house preparation.

KEYWORDS:
^{225}Actinium; PSMA; metastatic Castration-Resistance Prostate Cancer (mCRPC); quality control; radiopharmaceutical

INTRODUCTION

Metastatic Castration-Resistance Prostate Cancer (mCRPC) occurs when there is spread of prostate cancer in the body despite optimised pharmacological therapy and achieving castration levels of testosterone hormone to control the disease. Treatment is usually palliative at this point, however, the advent of using radiopharmaceuticals to treat mCRPC has brought new hope for improved progression free survival and overall survival. The development of mCRPC therapy has gone further from [^{177}Lu]Lu-PSMA-RLT to [^{225}Ac]Ac-PSMA-RLT since the establishment of [^{68}Ga]Ga-PSMA-11 as the theragnostic twin.[1,2] In prostate cancer, PSMA is overexpressed 100- to 1,000 times more than in normal cells, making it an interesting target for imaging and therapeutic tools and enabling this "image and treat" or also known as " treat what you see" strategy to become an important approach for personalised patients care.[3]

The use of [^{225}Ac]Ac-PSMA-RLT is found to be efficacious and safe for the treatment of mCRPC.[4] Following the Letter from Kleynhans & Duatti to EJNMMI Radiopharmacy and Chemistry volume 7, Article number: 23 (2022)[5] that has stated the interest and the number of clinical studies published on the use of [^{225}Ac]Ac-PSMA-RLT continue to increase in recent years. The main matter is largely related to the ''true'' molecular identity of 225Ac-radiopharmaceuticals. Generally, the molecular/chemical identity is confirmed using a reference standard containing a stable isotope of the radionuclide.

However, in the case of [^{225}Ac]Ac-radiopharmaceuticals, the lack of a stable isotope necessitates cross-validation methods using high-pressure liquid chromatography (HPLC) and thin-layer chromatography (TLC) methods. In addition, the radiochemical purity (RCP) of [^{225}Ac]Ac-radiopharmaceuticals can only be measured through its daughter product that emits photons; ^{221}Fr (^{218}keV) or 213Bi (^{440}keV), that is measurable until it reaches equilibrium after 6 half-life of both daughter nuclides. In practice, [^{221}Fr]Fr is commonly used for detection as the secular equilibrium between [^{225}Ac]Ac and [^{221}Fr]Fr can be achieved within 30 minutes post-radiolabelling, as depicted in Figure 1. Inherently, another issue with the use of [^{225}Ac]Ac radionuclides includes the nuclear recoil effect that causes the release of the daughter radionuclide from the radiopharmaceutical and may lead to unnecessary irradiation of other organs that may subsequently cause severe radiotoxic effects such as organ dysfunction.[6]

Nevertheless, the quality control practice in Malaysia for in-house preparation for [^{68}Ga]Ga and [^{68}Lu]Lu-labelled radiopharmaceuticals are generally radiochemical yield (RCY), radionuclidic purity and pH, neglecting the chemical identity of the labelled compound. The concern in the case of [^{225}Ac]Ac-labelled radiopharmaceuticals was due to the nuclear recoil effect that may cause radiolysis. Therefore, correct analytical methods are critical to identify free [^{225}Ac]Ac, [^{225}Ac]Ac-DTPA, radiolysed [^{225}Ac]Ac-labelled, and labelled [^{225}Ac]Ac-radiopharmaceuticals as presented in Figure 2. Hooijman et al. were able to separate and identify free [^{225}Ac]Ac, [^{225}Ac]Ac-DTPA, and labelled [^{225}Ac]Ac-radiopharmaceuticals, however, could not identify the radiolysed [^{225}Ac]Ac-labelled using the Radio-TLC method.[7]

The radiolysed [^{225}Ac]Ac-labelled radiopharmaceutical can only be analysed using the HPLC method, as illustrated in Figure 3. Due to the time required for equilibrium between [^{225}Ac]Ac and [^{221}Fr]Fr, a fraction collector is needed to do such an analysis.[8] The collected fractions are then measured using

This article was accepted: 27 September 2024
Corresponding Author: Subapriya Suppiah
Email: subapriya@upm.edu.my

Table I: Hazard Analysis and Critical Control Point (HACCP) Matrix for in-house [225Ac]Ac radiopharmaceutical preparation

Process Steps	Potential Hazard	Critical Limit	Risk Level	Corrective Action	Frequency
Receipt of Starting Materials					
Receiving of radionuclide source	Long live radionuclidic & radioisotopic impurities	Depending of [225Ac]Ac production route: i. ^{229}Th/^{225}Ac generator: • [^{229}Th]Th < 0.009% • [^{225}Ra]Ra < 0.002% ii. Irradiation of [232Th]Th (spallation reaction): • [^{227}Ac]Ac ≤2%	High	Check and verify the [^{225}Ac]Ac Certificate of Analysis (COA)	Each delivery
Receiving of precursors (Eg. PSMA, DOTA-TATE)	Risk of microbial contamination	• GMP grade • Quantity of precursors clearly stated	High	Check and verify the Certificate of Analysis (COA)	Each delivery
Receiving of other starting material (Eg. Ascorbic acid, DTPA solution, Sodium acetate buffer, Hydrochloric acid)	Risk of microbial and metal contamination	• GMP grade • Trace free metals • Quantity/Concentration	Moderate	Check and verify the Certificate of Analysis (COA)	Each delivery
Radiolabeling Process					
Addition of quenchers	Radiolysis effect	• Highly recommended to be added in critical steps such as radiolabeling and dilution	Moderate	personnel - ufficient amount of ascorbate is added - verified by secondary personnel - record in batch preparation record	Each preparation
Labeling Buffer	Unsuitable labelling pH resulted in low RCP	• Sodium Acetate buffer ~ pH 5 • Tris (hydroxymethyl) aminomethane buffer ~ pH 9	High	Documentation and personnel - correct buffer is use - verified by secondary personnel - record in batch preparation record	Each preparation
Heating condition *relevant for DOTA chelators	Low RCP and unlabeled [^{225}Ac]Ac	• Ensure correct temperature and time : dry bath incubator <100°C	High	Documentation and personnel - correct temperature and time - verified by secondary personnel - record in batch preparation record	Each preparation
Addition of DTPA to complex free [^{225}Ac]Ac in final product	Radiotoxic effect of daughter nuclide due to recoil effect	• to be added in final product	High	Documentation and personnel - sufficient amount of DTPA is added - secondary personnel must check that DTPA is added - check the COA for the correct amount of DTPA	Each preparation
Quality Control					
Time for analysis	Inaccurate analysis lead to wrong interpretation	• Ensure secular equilibrium is achieved ~ 30 minutes waiting time	Low	Documentation - Can be identified from preparation time and analysis time (more than 30 minutes)	Each preparation
Physical appearance pH analysis	Risk of viable and non-viable particulate contamination	• Clear, colourless and free of particulate matter	Low	- visual inspection behind lead glass	Each preparation

Table I: Hazard Analysis and Critical Control Point (HACCP) Matrix for in-house [225Ac]Ac radiopharmaceutical preparation

Process čteps	Potential Hazard	Critical Limit	Risk Level	Corrective Action	Frequency
pH analysis	Irritation at injection site	• pH range 4.5-5.5	Low	- pH paper or calibrated pH meter	Each preparation
Radiochemical Yield *ratio (%) between labelled and free [^{225}Ac]Ac and/or [^{225}Ac]Ac-DTPA	Risk of impurities (free [^{225}Ac]Ac) present in final dose	• Radiochemical yield (RCY) ≥ 98%	High	- perform using radio TLC	Each preparation
Osmolality	Introduce pain at injection site	• < 600 mOs/kg	Low	- perform using calibrated osmometer; - osmolality data can be provided by manufacturer	• Validation phase • Changes in formulation
Radiochemical Purity	Risk of impurities (radiolysed [^{225}Ac]Ac-compound) in final product	• Radiochemical purity (RCP) ≥ 95%	High	- perform using HPLC with fraction collector - HPLC data can be provided by manufacturer	• Validation phase • Changes in starting materials / preparation/ process / analytical equipment
Validation of the analytical method	Inaccurate analysis lead to wrong interpretation	Radio-TLC and HPLC • Specificity & Range • Accuracy • Precision • Limit of Detection • Limit of Quantitation	High High	- to be performed at initial stage / validation phase	• Validation phase • Periodically (eg. Performance Qualification)
Stability study	Risk of impurities (free [^{225}Ac]Ac and radiolysed [^{225}Ac]Ac) present in final dose over time	Over the specified period of study: • Radiochemical purity (RCP) ≥ 95% • Radiochemical yield (RCY) ≥ 98%		- stability study & report can be provided by manufacturer	• Validation phase • Changes in starting materials / preparation process /

a gamma counter, and the chromatographic separation is analysed.

Current situation and solution in Malaysia

The preparation of in-house radiopharmaceuticals follows a risk-based approach. Risk assessment is necessary to determine the level of validation when introducing a new radiopharmaceutical compound. Generally, therapeutic radiopharmaceuticals follow a stringent requirement. In addition, in this case where there is no individual monograph for [^{225}Ac]Ac-labelled radiopharmaceuticals, the validation of analytical method and stability study are required to be done initially before it is adopted into the clinical settings.[9] This is to ensure that the patient's safety is not compromised as the routine quality control test in local hospital radiopharmacy is based solely on three general tests. Table 1 represents the Hazard Analysis and Critical Control Point (HACCP) matrix that can be considered for in-house [^{225}Ac]Ac radiopharmaceutical preparation starting from receiving of [^{225}Ac]Ac until the quality control analysis of final [^{225}Ac]Ac-radiopharmaceutical preparation.

The RCP and RCY analysis validation for [^{225}Ac]Ac-labelled radiopharmaceuticals has been published using HPLC and Radio TLC methods. Therefore, to the utmost knowledge and the responsibility of the radiopharmacist to identify the method used for [^{225}Ac]Ac-labelled radiopharmaceutical preparation since certain analysis cannot be performed without sophisticated equipment. Identifying radiolysed [^{225}Ac]Ac-labelled using the HPLC method can be tedious without a fraction collector. The manual collection method can be done by disconnecting the outlet from the UV detector and collecting using vials separated by time per fraction (0.5 minutes, 1.0 minutes). However, this method may pose a risk of radiation exposure to the analyst. Thus, due to the lack of equipment, specifically, HPLC with a fraction collector, proper radiation protection procedures, including its documentation, are required to prevent unnecessary exposure to ionising radiation during [^{225}Ac]Ac radiopharmaceutical quality control analysis.

Nevertheless, radiolysis can be prevented with the usage of an appropriate and sufficient amount of antioxidant. Hence, proper procedure and documentation should be considered to

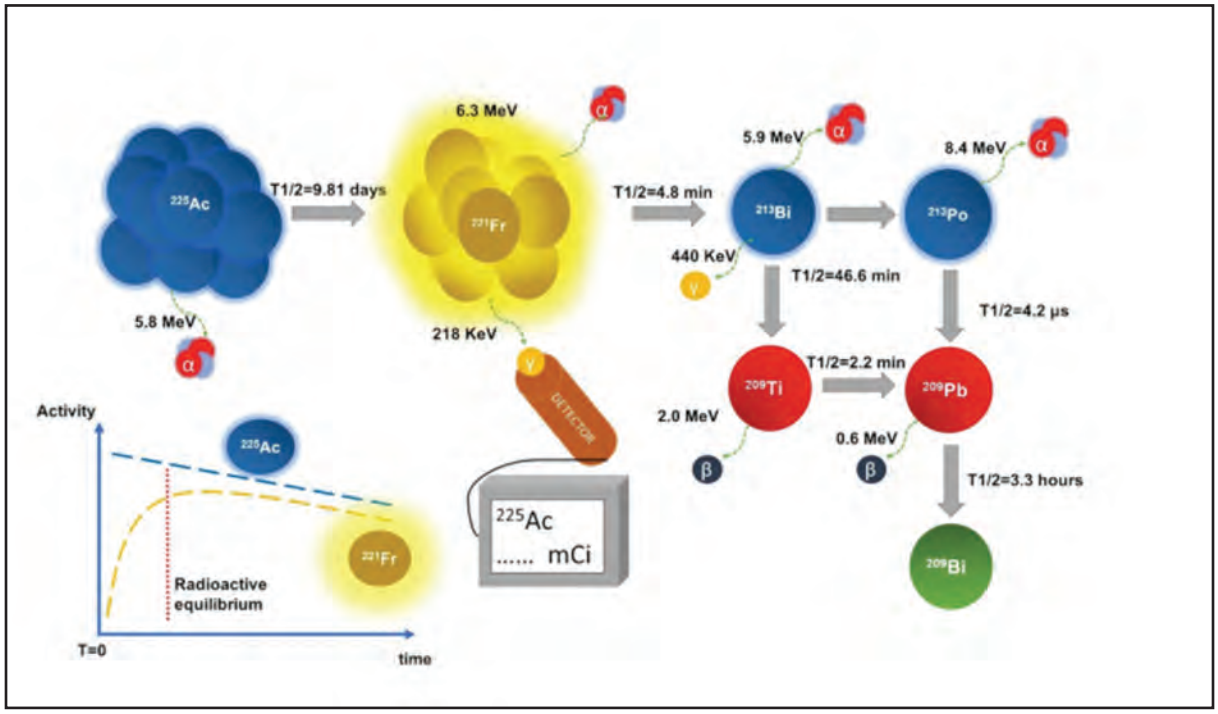

Fig. 1: Summary of the [^{225}Ac]Ac decay, which produces four alpha particles. The activity is measurable after radioactive equilibrium

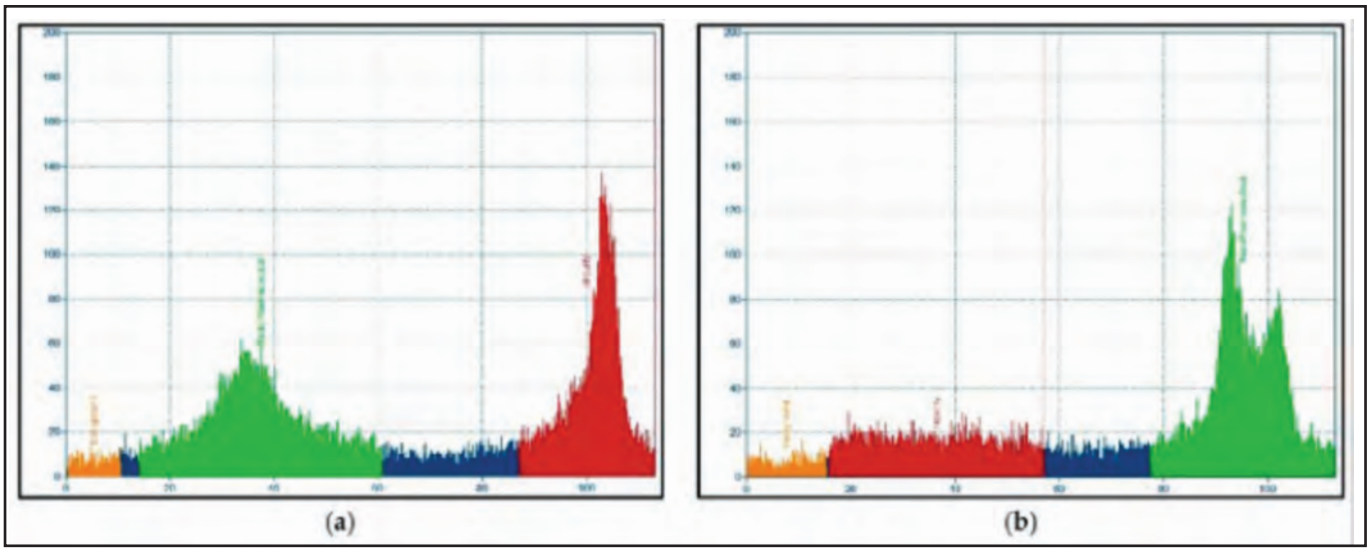

Fig. 2: Radio TLC analysis of [^{225}Ac]Ac and [^{225}Ac]Ac-DTPA, [^{225}Ac]Ac-PSMA-I&T using mobile phases sodium citrate (a) and acetonitrile/water (b). The colored chromatogram represents ([^{225}Ac]Ac-PSMA-I&T, green), impurity ([^{225}Ac]Ac and/or [^{225}Ac]Ac-DTPA, red), background orange), non-selected area blue). Adapted with from (Hooijman, Chalashkan et al. 2021)
The radiolysed [^{225}Ac]Ac-labelled radiopharmaceutical

ensure it is introduced in the preparation. This also applies to the peptide used for the preparation where wrong or insufficient peptide amount should be prevented as the molecular/chemical identity of [^{225}Ac]Ac-labelled radiopharmaceutical is not performed. The addition of DTPA to complex free [^{225}Ac]Ac is important to avoid the injection of free [^{225}Ac]Ac into a patient. Hence, this should also be documented as proof that it has been introduced during preparation.

A major challenge for [^{225}Ac]Ac radiopharmaceutical preparation is the ability to accurately quantify RCY and RCP given the time required for [^{225}Ac]Ac to reach secular equilibrium. Therefore, the limit of detection (LOD) and quantification (LOQ) for the analytical method should be defined to ensure that non-detectable free [^{225}Ac]Ac should be calculated based on the LOD or LOQ.

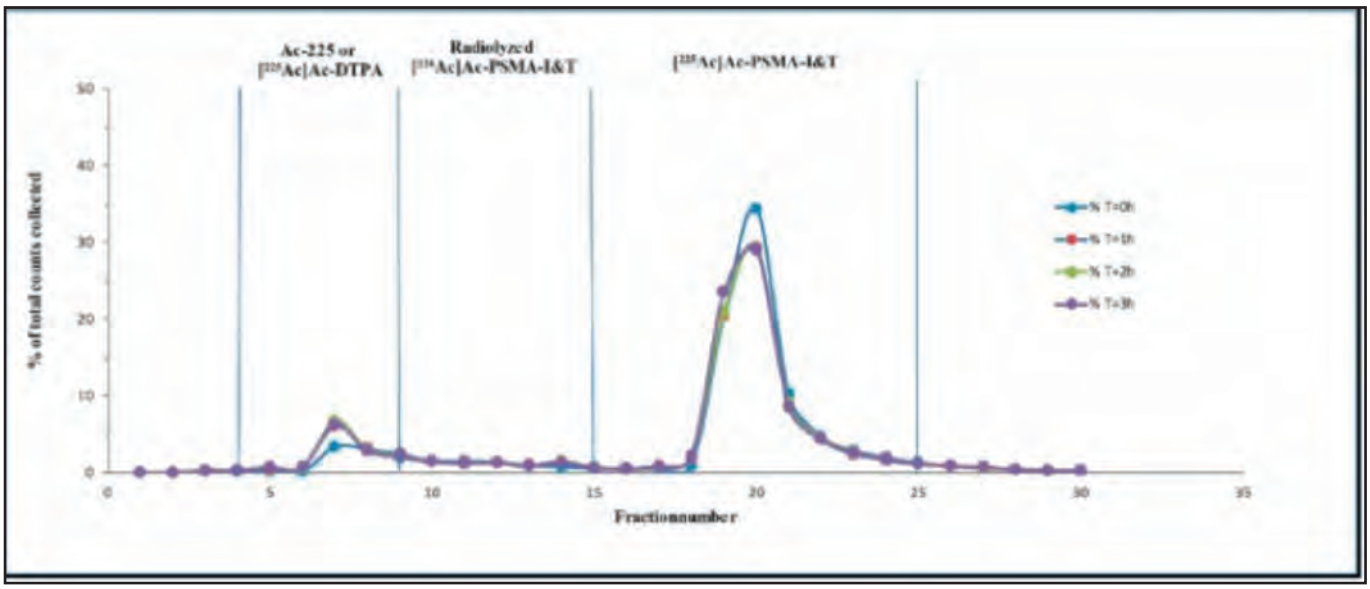

Fig. 3: HPLC fractions are measured using a gamma counter where the x-axis represents the fraction number based on [221Fr]Fr measurements and they-axis % of total counts, measured for 0, 1, 2, and 3 h: Non-optimized synthesis (RCY < 85%) with radiolysed [225Ac]Ac-labelled present in between peaks (10–15). Adapted with from (Hooijman, Chalashkan et al. 2021)

Extension of [225Ac]Ac-labelled radiopharmaceutical stability should only be considered after validation using HPLC. This is largely due to the possibility of an increase in radiolysed [225Ac]Ac -labelled present in the product. Thus, without a proper stability study, any [225Ac]Ac-labelled radiopharmaceutical should be discarded after expiration. Nevertheless, the need to extend the stability of [225Ac]Ac-labelled radiopharmaceutical can be prevented if patient preparation is done in a timely manner.

Furthermore, the outcome from the WARMTH Act study conducted on 488 men with mCRPC and a total of 1174 cycles of [225Ac]Ac-PSMA-RLT was a median overall survival of 15.5 months. Most importantly, no serious adverse events or treatment-related deaths were reported.[10] The most common adverse event was xerostomia as seen in other studies.[4] Nonetheless, ensuring the safety and efficacy of the [225Ac]Ac-labelled radiopharmaceutical preparation is critical. Such preparation should only be used in-house and approved by an authorized person.

CONCLUSION

The present work summarizes potential hazards and a practical approach for in-house preparation of [225Ac]Ac-labelled radiopharmaceutical using the Hazard Analysis and Critical Control Point tool. This document can also guide local authorities in documenting, evaluating, and approving the preparation procedure. In addition, closing the gap between research and clinical institutions should be considered to intensify the development of Targeted Alpha Therapy and other radiopharmaceuticals in Malaysia.

ACKNOWLEDGMENT

The authors wish to thank the Pharmacy Practice & Development Division, Pharmaceutical Services Programme and Medical Radiation Surveillance Division, Ministry of Health Malaysia for their keen support. This study has been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with a reference number NMRR-ID-22-00822-0NL. The authors would like to express our sincere gratitude to the research subcommittee of the Malaysian Society of Nuclear Medicine and Molecular Imaging (MSNMMI) for their expertise and support. We would also like to thank the Director General of the Ministry of Health Malaysia for his permission to publish this article.

REFERENCES

1. Ashhar Z, Ahmad Fadzil MF, Othman MF, Yusof NA, Abdul Onny M Mat Ail N, SF Abd Rahman. Cyclotron Production of Gallium-68 Radiopharmaceuticals Using the 68Zn(p,n)68Ga Reaction and Their Regulatory Aspects. Pharmaceutics 2023; 15(1): 70.
2. Ashhar Z, Ahmad Fadzil MF, Md Safee Z, Aziz F, Ibarhim U., Nik Afinde NMF, et al. Performance evaluation of Gallium-68 radiopharmaceuticals production using liquid target PETtrace 800 cyclotron. Applied Radiation and Isotopes 2024; 205: 111161.
3. Machado Rocha J. M., and Jorge Pereira B. A. G. Biological principles and clinical application of positron emission tomography-tracers in prostate cancer: a review. Prostate Int 2019; 7(2): 41-6.
4. Satapathy S, Sood A, Das CK, BR Mittal. Evolving role of 225Ac-PSMA radioligand therapy in metastatic castration-resistant prostate cancer—a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2021; 24(3): 880-90.
5. Kleynhans J, Duatti A. The determination of the radiochemical purity of Actinium-225 radiopharmaceuticals: a conundrum. EJNMMI Radiopharm and Chem 2022; 7(1): 23.

6. Kozempel J, Mokhodoeva O, Vlk M. Progress in Targeted Alpha-Particle Therapy. What We Learned about Recoils Release from In Vivo Generators. Molecules 2018; 23(3): 581.
7. Hooijman EL, Chalashkan Y, Ling SW, Kahyargil FF, Segbers M, Bruchertseifer F, et al. Development of [(225)Ac]Ac-PSMA-I&T for Targeted Alpha Therapy According to GMP Guidelines for Treatment of mCRPC. Pharmaceutics 2021; 13(5): 715.
8. Kelly JM, Amor-Coarasa A, Sweeney E, Wilson JJ, Causey PW, Babich JW. A suitable time point for quantifying the radiochemical purity of 225Ac-labeled radiopharmaceuticals. EJNMMI Radiopharm and Chem 2021; 6(1): 38.
9. Gillings N, Hjelstuen O, Behe M, Decristoforo C, Elsinga PH, Ferrari V, et al. EANM guideline on quality risk management for radiopharmaceuticals. EJNMMI 2022; 49(10): 3353-64.
10. Sathekge MM, Lawal IO, Bal C, Bruchertseifer F, Ballal S, Cardaci G. Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study. The Lancet Oncol 2024; 25(2): 175-83.

COMMENTARY

Take C.A.R.E of patient safety: A call to action

Alex Ren Jye Kim, MHA[1], Keng Sheng Chew, PhD[2], Hie Ung Ngian, MPH[1]

[1]Sarawak General Hospital, Sarawak, Malaysia, [2]Universiti Malaysia Sarawak, Kuching, Sarawak, Malaysia

ABSTRACT

In a dynamic healthcare environment, patient safety is crucial. A "Conscious Actions Reduce Errors" (C.A.R.E) approach is needed to safeguard safety and reduce medical errors. The dual process theory highlights two thinking modes: intuitive (fast, automatic) and analytical (slow, deliberate). Intuitive thinking, though quick and often effective, can lead to cognitive biases like anchoring and availability heuristics. A C.A.R.E approach incorporating tools like the TWED checklist (Threat, What if I'm wrong? What else?, Evidence, Dispositional factors) and Shisa Kanko (Japanese method of pointing and calling) can help to improve decision-making and action precision in clinical settings.

KEYWORDS:
Patient safety, cognitive biases, Shisa Kanko, metacognition, medical errors

INTRODUCTION

In today's fast-paced and ever-evolving healthcare services, the imperative to prioritize patient safety cannot be overstated. The quote, *"Nothing we do is so important that we cannot take the time to do it safely,"* encapsulates the essence of what should be a universal guiding principle in medical practice. It underscores the critical need to adopt a "Conscious Actions Reduce Errors" (C.A.R.E) mindset that can serve as an overarching framework to enhance patient safety.

The World Health Organization (WHO) has long championed the cause of patient safety. This commitment is reflected in its annual event of World Patient Safety Day on 17 September, which aims to raise awareness and drive global action on patient safety issues. The theme for World Patient Safety Day 2024, "Improving Diagnosis for Patient Safety," with the slogan "Get it right, make it safe!" is particularly significant.[1] It highlights the crucial role of accurate diagnosis in ensuring patient safety and the need for healthcare professionals to adopt best practices to minimise diagnostic errors.

Medical errors are a significant concern in healthcare, often leading to adverse outcomes and compromised patient safety. They can arise from various factors, in which cognitive biases are one of them. Research evidence supports the notion that decision-making, including clinical diagnosis, can be influenced by our two modes of thinking processes as described in the dual process theory of thinking.[2]

The dual process theory posits that there are two modes of thinking.[2,3]

Mode 1 (Intuitive): Fast, automatic, and subconscious.
Mode 2 (Analytical): Slow, deliberate, and conscious.

In clinical settings, Mode 1 allows healthcare professionals to quickly recognise patterns and make rapid decisions based on experience and intuition. However, this can also lead to cognitive biases and errors. Common examples of cognitive biases, which operate at a subconscious level, that can significantly affect diagnostic accuracy include:

Anchoring Bias: This occurs when a clinician relies too heavily on the initial piece of information (the "anchor") and fails to adjust their thinking as new information becomes available[2,3]
Availability Heuristic: This bias involves making decisions based on how easily information comes to mind, or "mental shortcuts". For instance, a doctor might diagnose a condition he/she has seen frequently recently, rather than considering other possibilities.[2,3]

Addressing these challenges requires a "conscious" approach that encompasses metacognition and proven safety techniques. In this context, the concept of C.A.R.E, the TWED checklist[2,3], and the practice of Shisa Kanko[4,5] offer valuable tools and strategies to enhance diagnostic accuracy and patient safety.

Conscious actions reduce errors (C.A.R.E)

Ensuring patient safety begins with mindfulness and intentionality in every aspect of patient care. The concept serves as a reminder that vigilance and careful verification are crucial at every stage of patient management. This approach goes beyond mere technical accuracy.

Additionally, C.A.R.E symbolises a commitment to patient safety through deliberate and conscious actions. Every process, no matter how routine, must be executed with an acute awareness of its potential impact on patient outcomes. This ethos fosters a culture of safety where healthcare professionals are consistently reminded of their responsibility to act thoughtfully and conscientiously.

Indeed, an extra few seconds of proper checking does make a difference! This small investment of time ensures that important pieces of information are verified and double-checked before proceeding, which can potentially prevent significant errors. The idea of taking an extra moment to

This article was accepted: 11 September 2024
Corresponding Author: Keng Sheng Chew
Email: kschew@unimas.my

confirm actions aligns perfectly with the concept of C.A.R.E, emphasising that mindfulness is a critical component of patient safety.

The TWED checklist: facilitating metacognition and improving diagnosis

Metacognition, the practice of reflecting on one's thought processes[3], is a crucial skill for making clinical diagnoses. The TWED checklist is an instrumental tool designed to enhance this reflective practice by systematically addressing key aspects of decision-making.[2,3] The components of the TWED checklist are as shown in Table I below.

The implementation of TWED checklist can foster a thorough and reflective approach to patient care and prompts clinicians to consciously evaluate their decisions in order to reduce diagnostic errors, improve patient safety, and minimize risk of oversight in clinical judgment.

Shisa Kanko: pointing and calling to mitigate human errors

Shisa Kanko, a safety technique originating from Japanese railway operations, has demonstrated efficacy in reducing human error through the method of pointing and calling.[3] This practice entails physically pointing at the pertinent pieces of information and verbally affirming them. When translated to healthcare, Shisa Kanko can significantly enhance focus and verification processes, such as during medication dispensing and administration or handling blood products.

Research evidence supports the effectiveness of Shisa Kanko in reducing errors. Indeed, a study conducted by the Japanese railway industry demonstrated that implementing Shisa Kanko led to a six-fold reduction in errors.[3] This remarkable decrease underscores the potential of this technique in improving accuracy and safety in various settings, including healthcare.

The act of pointing and verbal confirmation, which engages multiple sensory modalities - visual, auditory, and kinesthetic[4,5], can significantly enhances concentration and accuracy through the activation of the prefrontal and visual cortex.[6] By integrating Shisa Kanko into daily routines, healthcare workers can reduce errors caused by distraction or routine complacency.[4] This method fosters a heightened state of awareness and mindfulness, contributing to a safer clinical environment.

Combining TWED checklist and Shisa Kanko as a unified C.A.R.E. tool

Combining the TWED checklist (a cognitive tool for "checking on our thinking") and Shisa Kanko (a psychomotor skill for "checking on our doing") into a unified C.A.R.E. tool can safeguard clinical decision-making and precision of actions in clinical settings. Starting from the constellation of patient's data, a physician generates a list of probable diagnoses, which can be subjected to an iterative metacognitive screening using the TWED checklist to reduce cognitive biases. A treatment plan is then implemented to manage the working diagnosis. Shisa Kanko is performed by physically pointing to and verbally confirming key actions to enhance focus and accuracy (Figure 1).

Case illustration on the application of TWED checklist and Shisa Kanko

Just before handover in a chaotic emergency department, an unconscious 30-year-old polytrauma patient was brought in. Recognizing traumatic brain injury (TBI) as a threat (T), a CT brain scan was ordered. Considering what else (W) the patient might have sustained; a CT cervical scan was also

Table I: TWED Checklist Components and Explanation

T - Threat	Identifying potential threats (e.g.: considering worst-case scenario) to patient safety in any given situation.
W - What if I am wrong? What else	Challenging assumptions and ensuring all possible diagnoses and contributing factors have been considered.
E - Evidence	Evaluating whether there is sufficient and robust evidence to support the diagnosis or clinical decision.
D – Dispositional factors	Recognising how emotion and environmental factors may influence decision-making

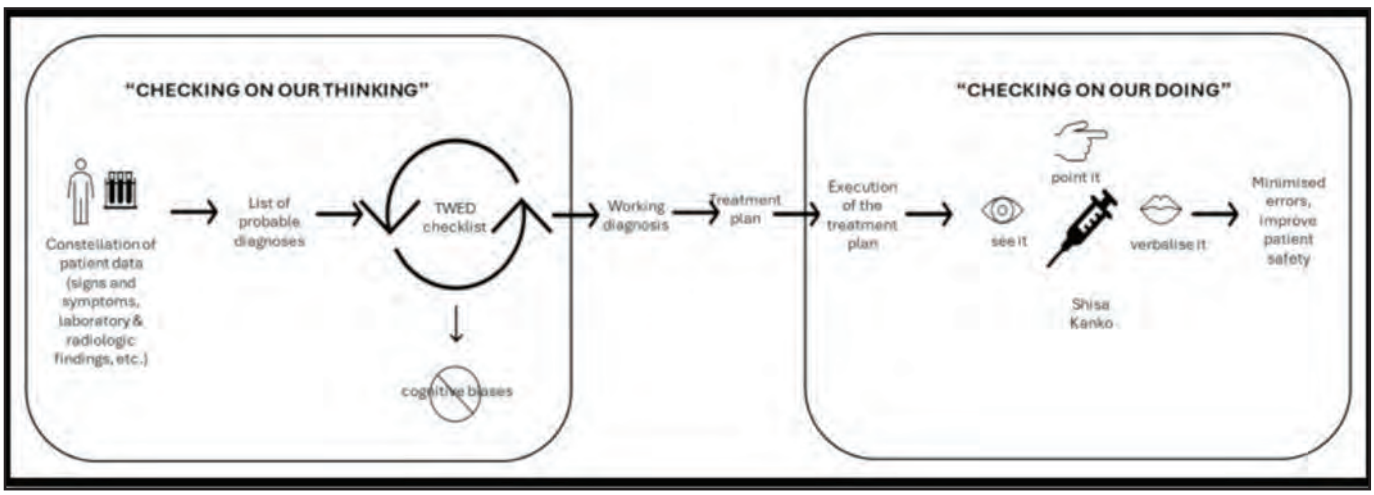

Fig. 1: Diagrammatic representation of combining TWED checklist and Shisa Kanko as a Unified C.A.R.E tool

performed as evidence (E) despite a clear X-ray. The fatigued night shift doctor, acknowledging his dispositional (D) factor, handed over to the morning shift. The patient, later found in hypovolemic shock, received whole blood. Before administering the blood product, the nurse utilised the Shisa Kanko method by pointing to the wristband and verbalising the patient identifiers (full name and identification number). Immediately afterwards, the nurse pointed to the blood product label and again verbalised the patient identifiers, ensuring the correct identification of the patient. This method is also applied to the process of checking blood grouping and the administration of medications to ensure accuracy.

CONCLUSION

Patient safety requires continuous vigilance and proactive measures. By implementing C.A.R.E, medical errors can be reduced, and patient safety can be enhanced to foster a culture of mindfulness, thoroughness, and accountability. The message is clear: "Nothing we do is so important that we cannot take the time to do it safely." As we celebrate World Patient Safety Day 2024, reaffirming the commitment to "First, Do No Harm" is therefore, essential.

ACKNOWLEDGEMENT

The authors wish to express their gratitude to Universiti Malaysia Sarawak for its support in the publication of this manuscript. We also extend our sincere thanks to the Director General of Health Malaysia for granting permission to publish this article.

REFERENCES

1. World Health Organization (WHO). The theme for World Patient Safety Day 2024, "Improving Diagnosis for Patient Safety," with the slogan "Get it right, make it safe!" 2024 [cited June 2024). Available from: https://www.who.int/news-room/events/detail/2024/09/17/default-calendar/world-patient-safety-day-17-september-2024-improving-diagnosis-for-patient-safety
2. Chew KS. 2024. Applying the Art of War in the Battle for Patient Safety. UNIMAS Publisher.
3. Chew KS, Durning SJ, van Merriënboer JJ. Teaching metacognition in clinical decision-making using a novel mnemonic checklist: an exploratory study. Singapore Med J 2016; 57(12): 694-700.
4. Violato E, Chao ICI, McCartan C, Concannon B. Pointing and calling the way to patient safety: An introduction and initial use case. J Patient Saf Risk Manag. 2022; 27(2): 86-93.
5. Tsang LF, Tsang WY, Yiu KC, Tang SK, Sham SYA. Using the PDSA Cycle for the Evaluation of Pointing and Calling Implementation to Reduce the Rate of High-Alert Medication Administration Incidents in the United Christian Hospital of Hong Kong, China. J Patient Saf Qual Improv. 2017; 5(3): 577-83.
6. Kishi C, Nakano Y, Bhuiyan MS, Kawanaka H, Oguri K, editors. Verification of the effect on "Finger Pointing and Calling" method from observation of brain activity related driver's attention. 17th International IEEE Conference on Intelligent Transportation Systems (ITSC); 2014: IEEE.

Acknowledgement
November Issue 2024

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Dr Ahmad Shuyuti Nur Aini Syakirah
2. Dr Anthony Louis Kindu
3. Dr Azahari Kasbollah
4. Dr Azizi Abu Bakar
5. Dr Badrul Hisham Abd Samad
6. Dr Baharulhakim Said Daliman
7. Dr Balanathan Kathirgamanthan
8. Dr Cheng Hoon Chew
9. Dr Choon Seong Ang
10. Dr Davinder Singh Bagh
11. Dr Haryanto Haryanto
12. Dr Husna Ahmad Ainuddin
13. Dr Karimah Hanim bt Abd Aziz
14. Dr Liew Pek Kuen
15. Dr Mardiana bt Kipli
16. Dr Mau Ern Poh
17. Dr Mohd Aizuddin Abd Rahman
18. Dr Mohd Azmarul A Aziz
19. Dr Mohd Ihsanuddin Abas
20. Dr Mohd Nazri Ali
21. Dr Muhd Siv Azhar Merican Abdullah
22. Dr Navin Kumar Devaraj
23. Dr Peter Eu
24. Dr Rama Krishna Supramanian
25. Dr Rasidah Abd Wahab
26. Dr Shailendra Magdum
27. Asst Prof Dr Shatha Farouk Abdullah
28. Dr Siti Hafsah Abdul Halim
29. Dr Siti Husna Hussein
30. Dr Siti Khadijah Abdul Rahman
31. Dr Siti Nazira Abdullah
32. Dr Sufian Adenan
33. Dr Tanyaluck Thientunyakit
34. Dr Theodoros Aslanidis
35. Dr Tim Aung
36. Dr Titan Ligita