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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.

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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.

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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.
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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
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Original Articles

CONTENTS Page

Correlation of risk factors with systemic inflammatory response syndrome in burn patients at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia

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ABSTRACT

Introduction: Systemic inflammatory response syndrome (SIRS) is the main cause of death in burns and is associated with high burn mortality rates. SIRS occurs when burns are in the subacute phase and is affected by several factors, such as host, trauma and management. The research was conducted at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia, using retrospective observational analytic research design. The aim of the study was to assess the correlation of risk factors which include age, extent of burns, cause of burns, inhalation trauma, history of hyperglycaemia, anaemia, hypoalbuminemia and ESBL infection with the incidence of SIRS.

Materials and Methods: The study is observational analytic research using a retrospective design and secondary data of all burn patients treated at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia from January 2018 to December 2019.

Results: A total of 163 burn patients were included. Among comorbidities found were inhalation trauma (39.3%), diabetes mellitus (2.5%), anaemia (14.7%), hypoalbuminemia (40.5%) and ESBL infection (1.2%). A total of 11 patients (6.7%) suffered from SIRS. The statistical analysis showed that anaemia (p=0.012), hypoalbuminemia (p=0.030) and the percentage of burns (p=0.001) were significantly correlated to the incidence of SIRS while age, sex, cause of burn injury, inhalation trauma, diabetes mellitus and ESBL infection have no significant correlation with SIRS.

Conclusion: Burn surface area is the most influencing factor of SIRS incident. It is important to meticulously monitor patients with extensive burn areas for indications of SIRS. However, the sample size of this study was relatively small, and it used a retrospective approach, so a larger sample size and a prospective or cohort design method were recommended for further study.

KEYWORDS:
Risk factors, systemic inflammatory response syndrome, burn, Indonesia, preventable deaths

INTRODUCTION

Burn injuries represent one of the most severe forms of trauma, inflicting enduring physical and psychological distress. They cause immense suffering and can lead to significant disabilities, often resulting in societal stigma.[1] The impact of a severe burn injury extends beyond the immediate physical damage. It initiates a systemic chain reaction within the body, triggering a systemic inflammatory response syndrome (SIRS) and profound metabolic disturbances. These disturbances can present in various forms, including cardiac dysfunction, acute respiratory distress syndrome, acute renal failure and increased intestinal permeability, which can potentially lead to bacterial translocation.[2-4] Furthermore, the body's homeostatic balance is significantly disrupted, leading to conditions such as hypermetabolism, hypercatabolism and sepsis. These severe disruptions can escalate to multiple organ failure and, in extreme cases, result in death. Therefore, the repercussions of burn injuries are far-reaching, causing a cascade of complications that can have enduring consequences.

According to the World Health Organization (WHO), burns account for more than 300,000 deaths worldwide each year.(1) In Indonesia, the mortality rate from burns is particularly high, around 40%, with severe burns being the primary cause.6 This high mortality rate is closely associated with SIRS, which is the leading cause of death in burn cases, accounting for 47.05% of fatalities.[7,8] Specifically, at Dr. Soetomo General Hospital, the mortality rate for patients with burn injuries was 10.3% based on data from 2007 to 2011. Meanwhile, the Burn Center of Cipto Mangunkusumo Hospital reported a higher mortality rate of 24% between January 2013 and December 2015.[9,10]

SIRS is an exaggerate, complex and non-specific inflammatory response of immune system to condition that is harmful to the body.[11] SIRS is a problem that arises in the subacute phase of burns and is influenced by several factors, including host, trauma and management factors.[7] Until now in Indonesia, there has been no research correlating these factors with SIRS. This is the basis for conducting this study to know the correlation of risk factors which include age, the extent of burns, cause of burns, inhalation trauma, history of hyperglycaemia, anaemia, hypoalbuminemia and extended spectrum beta lactamase (ESBL) bacterial infection with the

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Table I: Characteristic of study participants

Characteristics	n	%	Mean	SD
Age (years)			34.48	21.00
Less than 1	11	6.7		
1-20	30	18.4		
21-60	101	62		
>60	21	12.9		
Sex				
Male	111	68.1		
Female	52	31.9		
Cause				
Fire	98	60.1		
Hot water	35	21.5		
Electricity	21	12.9		
Chemicals	4	2.5		
Hot oil	2	1.2		
Thermal contact	3	1.8		
SIRS incidence				
Occurred	11	6.7		
Not occurred	152	93.3		
Inhalation trauma				
Occurred	64	39.3		
Not occurred	99	60.7		
Diabetes mellitus				
Occurred	4	2.5		
Not occurred	159	97.5		
Anaemia				
Occurred	24	14.7		
Not occurred	139	85.3		
Hipoalbuminemia				
Occurred	66	40.5		
Not occurred	97	59.5		
ESBL infection				
Occurred	2	1.2		
Not occurred	161	98.8		
Burn surface area percentage				
Less than 50%	125	76.7		
50% or more	38	23.3		

SIRS = Systemic inflammatory response syndrome; ESBL = Extended spectrum beta-lactamase

Table II: Statistical comparison analysis of risk factors for Systemic Inflammatory Response Syndrome in burn patients admitted to the Burn Center of Dr Soetomo General Hospital

Variables	OR	95%CI	p-value
Age	-	-	0.412
Sex -	-	0.733	
Cause	-	-	0.725
Inhalation trauma	-	-	0.112
Diabetes mellitus	-	-	1.000
Anaemia	0.213	0.05, 0.81	0.012*
Hipoalbuminemia	0.231	0.06, 0.91	0.030*
ESBL infection	-	-	0.131
Burn surface area percentage	5.835	1.55, 21.95	0.001*

OR = Odds Ratio, 95%CI = 95% Confidence Intervals, ESBL = Extended spectrum beta-lactamase, *Statistically significant

incidence of SIRS in burn patients and the mortality rate at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

The study is observational analytic research using a retrospective design based on secondary data. The research sampling method used the total sampling method including data from all burn patients treated at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia. The following criteria was used as inclusion criteria: patients diagnosed with burn injury and admitted from 2018 to 2019. The data were extracted from medical records of the patients. The independent variables were age, extent and depth of burns, causes of burns, hyperglycaemia, anaemia, hypoalbuminemia and ESBL. The dependent variable (bound) is the occurrence of SIRS.

STATISTICAL ANALYSIS

The data is presented descriptively in the form of graphs and tables. The comparison of each variable was analysed using the chi-square statistical test or Fisher's exact test. All data were analysed using the Statistical Package for the Social Sciences (SPSS) software with a significance of 0.05.

RESULTS

The study included 163 burn patients at the Burn Center of Dr Soetomo General Hospital, Surabaya, Indonesia from January 2018 to December 2019. Table I displays the results of the descriptive analysis. The table shows that the study population was mostly from productive age (2060 year) with 101 patients (62.0%) and the mean age of sample in this study was 34.48±21.00 year. The most common cause of burn injury was fire (60.1%). The mean of burn surface area was 30.93±23.39%, where 125 patients had less than 50% of burn surface area. Sixty-four patients (39.3%) suffered from inhalation trauma, four patients (2.5%) had diabetes mellitus, 24 patients (14.7%) suffered from anaemia, 66 patients (40.5%) suffered from hypoalbuminemia and two patients (1.2%) suffered from EBL infection. Among them, 11 patients (6.7%) suffered from SIRS.

The result of the statistical analysis showed that anaemia, hypoalbuminemia and burn body surface percentage were significantly correlated to the incidence of SIRS while age, sex, cause of burn injury, inhalation trauma, diabetes mellitus and ESBL infection has no significant correlation with SIRS. The detail are shown in Table II.

The data processed consequently were analysed using logistic regression analysis resulting in burned body surface area percentage as the most influencing factor of SIRS incident (Odds Ratio, OR: 5.835; 95% Confidence Intervals, 95%CI: 1.55, 21.95), followed with anaemia (OR: 0.213; 95%CI: 0.05, 0.81).

DISCUSSION

SIRS is a form of systemic clinical response to various severe clinical stimuli such as infection and non-infection such as trauma, burns, autoimmune reactions, cirrhosis and pancreatitis. The inflammatory response following an injury is physiological. However, when this response is systemic, it cannot be considered physiological anymore.[12]

In burns patient, the predisposing factors for the emergence of SIRS are grouped into two factors: internal and external. Internal factors include the general state of the patient, such as age and nutritional status as well as other co-morbid conditions, including pregnancy, existing disease, or disorder such as heart disease, and kidney, vascular and other metabolic disorders. External factors include the type of trauma and its management. The types of trauma that play a role in the course of the disease and prognosis include inhalation injuries, shock, the extent and depth of burns, and other accompanying injuries. Meanwhile, management that affects the incidence of SIRS includes first aid given, resuscitation measures and further management, including wound care management.[12]

The previous study was conducted by Burman Hedi in 2017 with different samples and populations through correlation analytic research using observational methods and cross-sectional approaches to look at factors related to SIRS events including age, infection cases, cases non-infectious, surgical cases and non-surgical cases. The study population was patients treated in the intensive care unit (ICU) of Lahat Hospital, South Sumatra. The results showed that there was a significant relationship between age (p=0.009) gender (p=0.007), cases of infection (p=0.010) and surgical cases (p=0.014) and the incidence of SIRS.[13]

The findings of this study have significant implications for the clinical management of burn patients. The identification of burn area and anaemia as key risk factors for the incidence of SIRS provides clinicians with valuable information for early detection and intervention.

Given that the extent of a burn has been recognised as the most influential risk factor, it is imperative for healthcare professionals to meticulously monitor patients with extensive burn areas for indications of SIRS. This could necessitate more regular assessments and the utilisation of predictive instruments to evaluate the probability of SIRS occurrence.

Routine physical examinations and laboratory investigations can be employed to more effectively monitor these patients. Physical examinations can aid in the early detection of SIRS signs, such as alterations in body temperature, heart rate, and respiratory rate.[14,15] Persistent tachycardia, tachypnoea, leucocytosis and a resetting of normal temperature to approximately 38°C have been documented as indicators of SIRS in burns encompassing more than 15-20% of the total body surface area (TBSA).[16] Laboratory tests can also provide a more detailed insight into the patient's condition. For instance, blood tests can reveal abnormalities in the levels of certain biomarkers associated with inflammation and infection, such as C-reactive protein (CRP), procalcitonin (PCT) and interleukins (ILs). Therefore, a comprehensive approach to patient monitoring can significantly improve the management and outcomes of severe burn injuries.[17]

The TBSA implicated in a burn has been previously recognised as a determinant of fatality in patients suffering from severe burns. Research indicates that for each one percent escalation in TBSA burned, there is a corresponding six percent augmentation in the risk of mortality.[18] Patients with extensive burn areas are susceptible to hypovolemic shock, a condition precipitated by increased systemic capillary permeability and consequent protein leakage. However, the ramifications of a larger burn area are not confined to hypovolemic shock; it can also precipitate the onset of SIRS. Investigations have established that both SIRS and TBSA are substantial contributors to fatality in patients with severe burns.[19] Consequently, the magnitude of the burn area assumes a pivotal role, not merely in the immediate repercussions of the injury, but also in the genesis of systemic complications that can markedly influence the patient's prognosis.

Anaemia was identified as the second most influential factor. This suggests that maintaining optimal haemoglobin levels could potentially reduce the risk of SIRS in burn patients.[21] Clinicians could consider implementing strategies to manage anaemia, such as transfusion of whole blood, in patients with significant burns.[21] Although other studies suggest that anaemia in SIRS patients is the result of bone marrow blunting as a response to erythropoietin, mediated by inflammatory cytokines such as interleukin-1 and tumour necrosis factor. Thus, the anaemia is precedented by inflammatory processes, and not the contrary.[22] Capillary leak from increased endothelial permeability in severe burn injury led to transendothelial loss of albumin. Besides its oncotic effect, albumin has anti-inflammatory and antioxidant activities beneficial to burn patient and to reduce the severity of SIRS. On the other hand, the release of cytokines induced by SIRS (e.g. interleukin-1 and tumour necrosis factor-α) may cause an acute reduction of albumin during the first 24-48 h through increased capillary permeability and subsequently through depressive effect on interleukin-1 to mRNA involved in albumin production.[23,24] By managing these risk factors effectively, it is hoped that the incidence of SIRS in burn patients can be reduced, thereby improving patient outcomes. Future research could focus on developing specific protocols for the management of these risk factors in the clinical setting.

However, this study has some limitations. The sample size was small, and it used a retrospective approach. To enhance the study's reliability and generalisability, future research should consider increasing the number of participants. A larger and more diverse sample would provide more robust results. Instead of data from 2 years, data from a longer period of time is recommended.

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Factors contributing to patency after aneurysmorrhaphy and outflow repair in arteriovenous fistula aneurysm treatment

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ABSTRACT

Introduction: Vascular access-related aneurysms (VARA) are a complication of arteriovenous fistulas. Repair techniques have been described in the literature with varied outcomes.

Materials and Methods: We conducted a prospective cohort study on patients who had VARA repair over 41 months. The indication for repair was an aneurysmal arteriovenous fistula (AVF) at risk of haemorrhage or difficulty in cannulation. Pseudoaneurysms, infected AVF and bleeding VARA were excluded. All patients underwent outflow stenosis treatment when present, followed by aneurysmorrhaphy. They were monitored periodically over 12 months, measuring functional primary and cumulative patency and access flow. We studied the patient demography, access flow and presence of outflow stenosis. Access flow was measured from the brachial artery (Qa) as a surrogate using ultrasonography. A Kaplan-Meier survival analysis was used to predict the primary and cumulative patency at 12 months and factors contributing to 12-month patency were analysed.

Results: A total of 64 patients were recruited for this study, of whom 58 completed the study. Most of the participants were male (67%) with a median age of 45 years. Forty-six patients (79.3%) had brachiocephalic fistula (BCF) aneurysms. Thirty-nine (67.2%) had preexisting outflow stenoses that required intervention. All patients underwent an aneurysmorrhaphy, of whom 12% had a cephalic arch vein transposition due to severe stenosis. Primary patency at 12 months was 86%, whereas the cumulative patency rate was 95%. Patency was significantly associated with younger age and showed a positive trend with higher pre-intervention Qa. Symptomatic recurrent stenosis developed in 17.2% of the cohort.

Conclusion: Improving the patency of VARA entails the treatment of outflow stenosis and aneurysmorrhaphy. Surveillance is important to detect and treat recurrent outflow stenoses. The outcome is better among younger patients with pre-interventional access flow as measured in the brachial artery as a surrogate.

KEYWORDS:
Arteriovenous fistula, aneurysmal arteriovenous fistula, vascular access, aneurysm, vascular access-related aneurysm, aneurysmorrhaphy, outflow stenosis

INTRODUCTION

The incidence of end-stage renal failure in Malaysia is increasing at an alarming rate. Aneurysms at the access sites of arteriovenous fistulas (AVF) used for dialysis are among the morbidities of this disease. Vascular access-related aneurysms (VARA) are not uncommon, with reported incidences ranging from 5-60%.[1] This wide range may be attributed to the varying definitions of VARA used in the literature. VARA is defined as a localised dilatation of the access vessel involving all wall layers, and a common threshold is 18mm.[2] Aneurysms develop due to a combination of high wall shear stress (WSS) induced by high flow, outflow stenosis and wall weakening due to multiple cannulations.[1,3]

Most VARA are asymptomatic and do not require any intervention. However, up to 31% of VARA require surgery due to haemorrhage or dysfunction.[4] Both European Society of Vascular Surgery (ESVS) and National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend surgical revision in symptomatic VARA.[5,6] Balaz et al., conducted a meta-analysis on VARA repair, either with aneurysmorrhaphy alone or combined with staplers or the use of sizing mandrels.[7] They found that the 12-month primary patency rate was 45-95%, with a pooled rate of 82%.[7] We are reporting the results of VARA repair at our centre, and studied the factors contributing to patency in our series.

MATERIALS AND METHODS

This was a prospective study of adult patients who underwent VARA repair over 41 months, from 1st July 2017 to 31st November 2020, at Kuala Lumpur Hospital (HKL), Malaysia. Our study received ethical approval from the National Medical Research and Ethics Committee (NMRR ID-23-00037-IVH). All patients with native VARA and an unhealthy access vessel wall at the risk of rupture were included. These

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included VARA with ulcers with eschar or thinned overlying skin. These patients were referred to our clinic from their respective dialysis centres because of concerns about rupture. Thinned skin was defined as white paper-like skin with loss of subcutaneous fat and normal tissue turgor due to scarring. Patients with pseudoaneurysms, infected fistulas, bleeding VARA, or those who presented with a herald bleed were excluded. In contrast to true aneurysms (VARAs), pseudoaneurysms have a wall defect and are more commonly associated with arteriovenous grafts. We excluded pseudoaneurysms because their pathophysiology is different, and the diseased segment is usually short. All procedures used to treat preexisting peripheral and central outflow stenoses were recorded. Outflow stenoses were categorised into two: central vein (axillary, subclavian, brachiocephalic vein and superior vena cava) and cephalic arch stenoses. All patients underwent preoperative Doppler ultrasound examination to measure the access flow at the brachial artery (Qa1) as its surrogate marker.[8]

All patients underwent central venography under local anaesthesia. Patients with flow-limiting outflow stenoses underwent angioplasty repair using a noncompliant balloon catheter. If complex cephalic arch stenosis was detected, cephalic to axillary vein transposition (CAT) was performed before VARA repair. Patients with central venous occlusion that was not amenable to angioplasty underwent surgical venous bypass. All the patients received a temporary dialysis catheter (TDC) on the contralateral side.

All procedures were performed with consent under general anaesthesia and prophylactic antibiotics without systemic heparin. The scarred or ulcerated skin was excised while creating a cutaneous flap. The venous limb was mobilised and a combination of aneurysmectomy and aneurysmorrhaphy was performed depending on the aneurysm length. Aneurysmectomy was performed between the clamps using the back-wall technique with polypropylene 5/0-6/0 sutures.

During aneurysmorrhaphy, the AVF inflow was clamped temporarily before clamping the aneurysmal segment longitudinally along the venous limb axis. These clamps were applied at a level to match the proximal and distal non-aneurysmal venous limb segments, after which the inflow clamps were released. The excess aneurysmal venous wall was resected above the clamps, leaving a cuff for aneurysmorrhaphy anastomosis in two layers. The repaired vessel was then anchored laterally with the ends of the suture to the bed without overt twisting to allow the native wall to lie anteriorly beneath the cutaneous flap.

Completion venography was performed, and any residual flow-limiting stenosis was repaired endovascularly. The wound was closed with a vacuum drain. Patients were observed in the ward for one week and dialysed using TDC. The TDC was removed after discharge once the repaired VARA was successfully used.

Assessments were made at 2 weeks and 1, 4, 6, and 12 months after surgery by measuring access flow wound and aneurysm recurrence. Qa2 was defined as the last access flow measured during the follow-up. A central venogram was performed if there was clinical suspicion of outflow stenosis and the patient was treated accordingly. Cumulative patency was defined as the time from successful AVF cannulation after VARA repair until access abandonment/end of the study. Primary patency was defined as the time until intervention to maintain patency. Both parameters were measured in months along with the type of intervention.

Statistical analyses were performed using the IBM SPSS Statistics (version 26). Categorical variables were analysed using Fisher's exact test, whereas continuous variables were analysed using the Mann-Whitney U test against a binary outcome and we accepted a p-value for statistical significance of ≤0.05. Kaplan-Meier survival analysis was used to estimate primary and cumulative patency rates.

RESULTS

Over the study period, 64 patients were recruited for the study. Of these, 58 were included in the final analysis. Six patients were excluded from the analysis due to loss to follow-up (4) and deaths unrelated to surgery (2). There were 39 men (67.2%), and the median age of the cohort was 45 years (range=20-75 years). Most of the VARA configurations were BCF (79.3%), and the median fistula age was eight years. The median access flow (Qa1) was 2.2L/min, whereas <7% had a flow of less than 1L/min. None of the patients showed clinical evidence of high-output heart failure. All patients in our cohort had Valentini type 3 VARA with thinned skin or superficial ulcers.[5] The decision regarding the risk of rupture was at the discretion of the operating surgeon. Thirty-nine patients had pre-existing outflow stenosis that required intervention (67.2%), of which 61.5% were at the cephalic arch and 19.0% required surgical reconstruction either by CAT or surgical venovenous bypass using a polyester graft. Most outflow stenoses were associated with BCF (87.2%), and all venovenous bypasses were performed for BCF VARA associated with central occlusion (Table I).

Recurrent outflow stenosis developed in ten patients who were treated with balloon angioplasty. No recurrence of VARA ulcers or skin thinning was observed during the 12-month surveillance period. We performed a sub-analysis of access flow before and after intervention (Qa1 and Qa2), defining high flow as >2L/min, which was present in 61.3% of the cohort before repair. As a large number of these patients had follow-up via telehealth (38.9%), we were unable to record their respective Qa2 and did not proceed with the sub-analysis. Among those who attended the clinic in person (n=22), flow reduction was observed in 63.6% of the patients.

The complications were monitored during the study period. Perioperative access thrombosis developed in 3.5% of patients, occurring in two patients with prior complex outflow intervention. One patient had a cephalofemoral vein bypass created to treat central venous occlusion a month before, whereas the second underwent a CAT and central vein PTA. Both patients underwent perioperative thrombectomy and their access remained patent after 12 months. One patient had a postoperative haematoma that

Table I: Demographic and intervention of VARA repair cohort

Characteristics (n=58)	n (%)	n (median) (interquartile range)
Patient age,years		45 (26) (range 20-75)
Gender		
Male	39 (67.2)	
Female	19 (32.8)	
Age of fistula, years		8 (5) (range 2-19)
VARA configuration		
BCF	46 (79.3)	
BBF	6 (10.3)	
RCF	6 (10.3)	
Pre-intervention brachial artery flow as a surrogate for access flow, L/min		2.2 (1.7) (range: 0.6 to 3.9)
Total outflow stenosis	39 (67.2)	
Central outflow stenosis	15	
Treatment modality		
Central conventional balloon venoplasty	11	
Vein-vein bypass	4	
Cephalic arch stenosis	28	
Treatment modality		
CAS conventional balloon venoplasty	21	
CAT	7	
TDC time, week	3 (0)	

Note: BCF = brachiocephalic fistula; BBF = brachiobasilic fistula; RCF = radiocephalic fistula; CAS = cephalic arch stenosis; CAT = cephalic arch transposition; VARA = vascular access related aneurysm; TDC = temporary dialysis catheter.

Table II: Comparison between the demographic data and cumulative patency at 12 months of repair

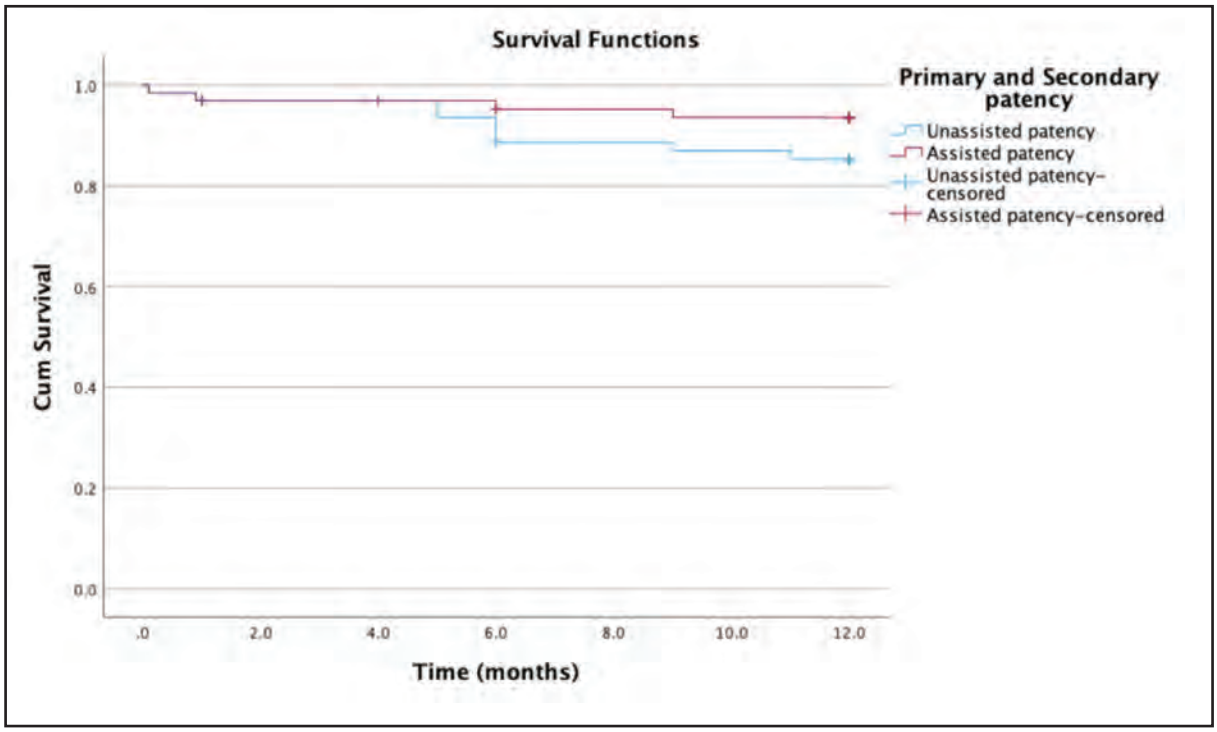
Characteristics	Loss of access n(%) (n=3)	Cumulative patency n(%) (n=55)	p-value
Patient age, year (median)	68.50 (9.19)	44.03 (13.99)	0.02
Gender			
Male	1 (2.6)	38 (97.4)	0.25
Female	2 (10.5)	17 (89.5)	
Age of fistula, year (median)	7.50 (3.54)	7.67 (3.39)	0.95
Fistula configuration			
BBF	0	5 (9.1)	0.44
BCF	2 (66.6)	46 (83.6)	
RCF	1 (33.4)	4 (7.3)	
Fistula flow, L/min (median)	1.15 (0.78)	2.43 (1.06)	0.08
Outflow stenosis	3	36	0.54
Thrombotic event	0	2 (3.64)	1

Note: BCF = brachiocephalic fistula; BBF = brachiobasilic fistula; RCF = radiocephalic fistula. The p-values reported are from univariate analysis.

Table III: Comparison of VARA aneurysmorrhaphy/aneurysmectomy results in the literature

Study	Year	n	Mandrel used	CVS before VARA repair -%	High Qa before VARA repair-%	Unassisted Patency 1y-%	Assisted Patency 1y-%
Hossny et al.[21]	2014	14	yes	Excl.	29*	NA	86
Nezakatgoo et al.[22]	2018	102	yes	NA	NA	NA	NA
Wan et al.[23]	2019	41	yes	Excl.	NA	95	100
Woo et al.[12]	2010	19	yes	20	NA	92.9	NA
Shigala et al.[24]	2014	31	yes	68	29***	65	74
Almehmi et al.[25]	2012	36	no	NA	NA	NA	NA
Patel et al.[10]	2015	48	no	90	NA	73	100
Wang et al.[11]	2017	185	no	71	8**	45	98
Our study		58	no	67	60**	84	94

Note: VARA = venous access-related aneurysm, Qa = access flow, CVS = central venous stenosis, 1y = 1 year, NA = not applicable. *High flow was defined as >1.5L/min. **High flow was defined as >2L/min. ***High flow associated cardiac failure



Time (Months)	0	4	6	12
Number at risk: primary	64	59	52	50
Number at risk: cumulative	64	59	56	55

Fig. 1: Kaplan-Meier curve showing cumulative and primary patency of VARA after repair over 12 months.

required emergency evacuation and haemostasis and the AVF was salvaged. No catheter-related bloodstream infection events were associated with TDC.

Kaplan-Meier survival analysis at 6 and 12 months showed that the primary patency rates were 88.7% and 85.3%, and the cumulative patency rates were 95.2% and 93.5%, respectively (Figure 1). One patient died from a cardiac event during the postoperative period and the second after surgery for intestinal obstruction five months after VARA repair, resulting in an adjusted 1-year patency of 94.8%, a 3-day mortality rate of 1.7%, and an overall mortality rate of 3.4% during the 12-month study period. We found that repaired VARA among younger patients (median age = 44 years) was statistically more likely to remain patent for one year (p=0.02). VARA with a higher access flow was more likely to remain patent one year after repair, although the difference was not statistically significant (p=0.08) (Table II). All the repaired VARA with high Qa1 were patent at 12 months, excluding two due to loss of follow-up.

DISCUSSION

There are various techniques for VARA treatment, although the principles should include exclusion of the aneurysm to reduce the risk of rupture, treatment of outflow stenosis to reduce recurrence, and improvement of access to real estate, as most VARA have unhealthy overlying skin and are tortuous. Strategies employed in VARA repair include external prosthetic mesh, staplers, grafts or mandrels.[7] Synthetic grafts offer shortened operative time but are associated with poor patency.[9] Staplers offer the benefit of speed, however, the device cost is a deterrent in our centre. Relining VARA with stent grafts has been described, though issues with sizing, seal and cannulation relegate this modality as a temporising measure instead.[5] Our experience in repairing VARA has led us to practice aneurysmorrhaphy, as it does not use a prosthetic graft and is cost-saving with regards to operative consumables.

The patency rate of our series compares favourably with the literature on VARA aneurysmorrhaphy.[7] We identified two studies that had similar patient characteristics (Table III). In the series by Patel et al., they selectively performed single- or two-stage repairs after routine fistulography,[10] whereas Wang et al., performed partial aneurysmectomy for all their VARA patients.[11] Both groups had a high proportion of outflow angioplasty, although they did not have many high-flow VARA. In a report by Wang et al., most angioplasties before and after VARA repair were for stenosis at the cephalic arch (33% and 23%, respectively).[11] Both studies reported far lower rates of TDC (2% and 23%, respectively) compared to our study. Neither categorised the VARA morphology, and it is most likely that those that required TDC had a complex VARA, that is, type 3. Sigala et al., found a similarly high proportion of outflow stenosis, though their repair employed a mandrel.[3] Woo et al., reported excellent primary patency rates in their cohort, although a surprisingly small proportion of patients had outflow stenosis.[12] All other studies on VARA aneurysmorrhaphy either excluded or did not detail the central stenosis.

In this report, we highlight the role of access flow and outflow stenosis in the pathogenesis of VARA. In the literature, outflow stenosis is present in 78% of VARA, whereas the incidence in our cohort was 67%. The location of stenoses varies depending on the AVF configuration.[13] Treating these stenoses reduces recurrence and aids in wall integrity during aneurysmorrhaphy by reducing the wall tension. We employed a similar approach to outflow stenosis as Patel et al.,[10] whereby all patients underwent a fistulogram before VARA repair.

Rajput et al.,[13] found that apart from the arm cephalic vein, most stenoses among BCF VARA were located at the cephalic arch. In our study, CAS was found in 85.3% of BCF VARA with outflow stenosis and 2.9 times more likely than a central disease. This preponderance is attributed to multiple factors including altered flow and WSS, extrinsic effects of the chest wall fascia, venous valves and possibly arch morphology.[14] In our experience, complex CAS is best treated with CAT as this also negates the effects of the chest fascia and arch morphology.[15] In our study, recurrent central stenoses were repaired with balloon angioplasty instead of stents due to cost and concerns of extrinsic compression with stent fracture and inadvertent coverage of collaterals.[5,6]

The second factor we highlight is the access flow. Sixty-one percent of our cohort had an access flow of more than 2L/min. High access flow promotes outflow stenosis and aneurysm formation.[16] Various techniques have been described to reduce fistula flow with the intent of reducing aneurysmal progression/recurrence.[17,18] Based on the literature, flow-limiting procedures should be incorporated in the repair of high-flow VARA. We found that VARA with high Qa1 tended to have better patency after aneurysmorrhaphy than those with Qa1 <1L/min (Table II).

A challenge in aneurysmorrhaphy is to estimate an appropriate neoluminal size. We employed an individual approach whereby the neolumen matched the outflow non-aneurysmal vessel, thus promoting laminar flow. An added benefit of avoiding mandrel use is prevention of prolonged vessel clamping and systemic anticoagulation. We avoided perioperative systemic heparin administration due to the risk of bleeding-related complications.[19] Our study had two intraoperative thrombotic events occurring after clamping, both among patients with complex outflow diseases. We currently employ a selective approach to systemic anticoagulation instead of not-at-all.

Given the complexity of treating VARA, detecting the disease at an earlier stage will improve patient morbidity and outcome. Primary prevention measures include avoiding 'general area cannulation' which is a known risk factor for developing AV aneurysms. Instead, healthcare personnel at dialysis centres should practice buttonhole or rope ladder techniques.[5] As discussed earlier, outflow stenosis is a risk factor for VARA and may manifest with raised venous pressure, prolonged bleeding from puncture sites after dialysis or a pulsatile AVF and patients with these signs should be referred by their primary physician or dialysis centre personnel. Late referrals may lead to aneurysm development, loss of access, rupture, and exsanguination. Early detection based on a high level of suspicion will expedite management, whereby the vascular access team can discuss with the patient treatment options, including salvage or creation of a new AVF while the existing AVF is still usable.

LIMITATIONS

Not all patients completed our face-to-face clinical surveillance because of logistics. Instead, many had telehealth follow-up. Others who were not contactable (6.0%) formed further bias due to the loss of follow-up. The statistical data in this study were analysed using univariate analysis. As the number of patients with loss of patency was low, we were unable to make accurate conclusions regarding the factors that contributed to this. Our findings were more likely to be affected by the treatment of outflow disease than by aneurysmorrhaphy. Finally, we were not able to control cannulation techniques, as they were performed in external centres.

CONCLUSION

VARA is highly associated with outflow stenosis and a high Qa. Good 1-year cumulative patency may be achieved among younger patients and those with higher pre-interventional brachial arterial flow, measured as a surrogate for access flow. The treatment strategy is multifaceted, and treating outflow disease is the cornerstone of managing VARA, whereas surveillance for recurrence is paramount. Early detection at dialysis centres can expedite earlier referrals and potentially salvage AVFs.

CONFLICT OF INTEREST

None

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Reasons behind providing care for older persons

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ABSTRACT

Introduction: There is a global increase in the ageing population, and Malaysia is expected to become an ageing country. As elderly individuals experience deterioration in physical and cognitive functions, they often require long-term care from caregivers. This study aims to investigate the reasons why caregivers provide care for older adults at home.

Materials and Methods: A qualitative phenomenological approach was employed, and semi-structured face-to-face interviews were conducted with 12 caregivers. Thematic analysis was used to identify patterns and themes in the data.

Results: Four master themes emerged from the analysis of the reasons for providing care to the older person by caregivers: personal factors needed by the elderly, personal factors of the caregivers, support from family members and friends, and environmental factors. Caregivers were motivated by the medical conditions of the older person, caregivers' sense of duty, and the desire to repay their elderly for their past care. Additionally, religious beliefs also played a role in motivating caregivers. Financial stability, knowledge and experience in caregiving, and the absence of other suitable caregivers were additional factors influencing caregiving decisions. Caregivers received support from family members, friends and sometimes hired help.

Conclusion: Cultural values, religious beliefs, and gender roles influence caregiving attitudes, emphasising the need for comprehensive understanding. Invaluable findings highlight the pressing need to comprehend the intricate dynamics, informing the development of tailored support systems. The study reveals that caregiving at home for the elderly is shaped by personal, social and environmental factors. Insight into these dynamics is crucial for robust support systems. By addressing the dimensions of caregiving, policymakers, healthcare professionals and society can better support caregivers in their essential role.

KEYWORDS:
Caring, older person, reason, phenomenology

INTRODUCTION

The global trend of the ageing population needs attention from all authorities. This trend is expected to continue in the coming decades, and Malaysia, in particular, is moving towards an ageing country. With ageing comes a range of challenges, including physical, psychological and cognitive decline, eventually leading to a dependency on others for daily activities. For instance, frailty and cognitive deterioration among the older person often result in falls, causing significant worry and requiring constant supervision from caregivers.[1] Consequently, the need for long-term care and support from caregivers becomes essential. A caregiver can be anyone: one who looks after a family member, partner or friend in need of assistance due to illness, frailty, disability or psychological issues and who cannot manage without their support.[2] Traditionally, the older person's care has been the responsibility of family members, as the extended family system has been deeply rooted in many societies for years.[3] As we move toward a community-based healthcare system, it is expected that a substantial portion of care for older adults will be provided within the home setting.[4] The World Health Organization emphasises the significance of home as a place of emotional and physical associations, memories, and comfort, reinforcing the importance of caring for older individuals in their own homes.[5] Caring involves taking on the well-being of another person and offering dedicated attention and support.[6]

Preliminary studies have identified various reasons why people choose to care for older individuals. Often, caregiving begins when the older person develops an illness or disability that impacts their ability to function independently. Long-term illness, disability or simply the challenges associated with ageing can significantly affect the lives of older individuals, making it difficult for them to manage daily tasks independently.[7] Some studies have found that caregivers are motivated by a desire to repay their parents for the care they received when they were young.

Caregivers recognise the sacrifices their parents made throughout their lives to provide them with the best possible care, and this acts as a strong driving force.[8] Taking care of ageing parents when they are sick and in need gives children a sense of fulfilment and serves as a way to express gratitude for their parents' selfless dedication.[9] Additionally, the emotions of care, the sense of duty and the interdependency between family members are common factors contributing to caring for older individuals.[10,11]

The need for providing holistic care plays a significant role in inspiring caregivers to provide support.[12-14] Participants in Northern California expressed their willingness to take on the role of a caregiver due to their deep commitment to holistic

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care for the person in need.[13] The profound sense of a holistic caregiving approach motivates caregivers and families to provide comprehensive support for their ageing loved ones. Caregivers often feel a strong responsibility since they understand the needs of their relatives better than anyone else.[15] It becomes their duty to pay attention to and care for the needs of their ageing parents. As parents age, the responsibility naturally falls on their children to ensure their well-being.[16]

However, some caregivers may find themselves lacking support, forcing them to shoulder the responsibility of caring for an older person alone. As the disease progresses, caregivers often find themselves in the position of providing care without significant assistance from other family members.[17] Despite their best intentions, other family members may struggle to offer help due to their own commitments.[18] It is commonly expected that unmarried individuals will take on caregiving responsibilities since they usually may have fewer responsibilities of their own. However, even married caregivers face the challenge of balancing their own family obligations while caring for their ageing parents. Caregivers may receive support from others during the caregiving journey. Even when the primary caregiver takes on the majority of the responsibilities, other close family members are often willing to lend a helping hand. Spouses or children within the same household typically provide the most assistance, but siblings, cousins and other relatives from different households also step in to provide support.[17]

Beyond family, caregivers may also find support from their friends.[17] Having someone to talk to about their caregiving experiences, whether it's a close friend or a fellow member of a support group, can be most valuable for caregivers.[17] Sons who care for parents with dementia, for example, demonstrate a willingness to take on the caregiving role and provide support to their parents.[17,18] In families where the husband is the head, the wife often takes on the caregiving responsibilities due to the other obligations of the husband. Furthermore, in cultures like Myanmar, caregiving is perceived as a duty primarily assigned to daughters, and elderly parents expect help and support from their daughters.[19] This cultural perception is widespread across many cultures worldwide, including Asian Indian contexts. Culture, encompassing a person's way of life and traditions, plays a significant role in shaping attitudes toward caregiving.

For instance, a qualitative study conducted in Kuala Lumpur, Malaysia, among 12 caregivers to patients with moderate to severe dementia, shed light on the cultural significance of caregiving among Chinese caregivers and its connection to the concept of filial piety.[20] The findings showed that Chinese caregivers perceive caregiving as a profound sense of duty or reciprocity deeply rooted in their cultural beliefs.[20] Similarly, Borrayo et al.,[21] explored the caregiving dynamics among 33 Spanish-speaking Latino caregivers in three states in the United States of America, namely Florida, Colorado, and Minnesota, and found that ethnicity and culture also influence caregiving structure in Latino communities.

Thus, the reasons behind caring for older individuals are diverse and complex. They encompass a sense of duty, reciprocation, the need to provide a holistic care and cultural expectations. Understanding these factors is crucial for developing effective support systems and interventions to assist caregivers in their vital role. As the global population continues to age, it becomes increasingly important to recognise and address the challenges faced by caregivers and provide them with the necessary resources and support to ensure the well-being of both the caregivers and the older individuals under their care.

MATERIALS AND METHODS

This research employed a qualitative phenomenological approach to gain insights into the reasons for caring for an older person at home. A total of 12 respondents meeting specific inclusion criteria, were purposively sampled for face-to-face semi-structured interviews. The study was conducted among four carers residing in Selangor, Melaka, and Johor. The inclusion criteria for the participants were as follows:

- Caregivers who provided support for elderly individuals aged 60 years and above in at least one Activity of Daily Living (ADL).
- Caregivers who provided care to the elderly at home for at least three months.
- Caregivers who could understand Bahasa Malaysia and English.

Thematic analysis was applied as the data analysis approach, which is a qualitative tool for identifying patterns or themes. This method is commonly used to recognise people's opinions, judgments, understandings, experiences, and values. According to Kiger and Varpio, there are six steps to follow when conducting a thematic analysis.[22]

Step 1: Familiarising yourself with the data
Step 2: Generating initial codes
Step 3: Searching for themes
Step 4: Reviewing themes
Step 5: Defining and naming themes
Step 6: Producing the manuscript.

The forward translation method was used to translate the quotes and themes from Bahasa Melayu to English. To protect their identity, participants were given pseudonyms when presenting the findings.

FINDINGS

Twelve Malay family caregivers participated in this study. Their ages ranged from 23 to 69 years, with two participants aged 60 years and above. The majority of the participants were females, and only one was male. Nine of the participants were still employed. The reasons for caring for an older person were analysed in this study and are presented in Table I. Four master themes of caregivers' reasons for providing care were identified: the personal factor of the elderly, the personal factor of the caregiver, the support of others and the environmental factor. This study found that the older people had at least one illness that could affect their ability to manage daily life, particularly if it impacted' their

Table I: Summary of master themes, themes and subthemes (n=12)

Master themes	Themes	Subthemes
1. Personal factors of elderly	1. Personal health status	• Medical illness • Physical, mental and psychological
	2. Self-care management	• Follow up • Safety • Inability to be independent • Pension
2. Personal factor of caregiver	1. Own wish	• 'I want to care and repay.' • Responsibility • Role model • Belief in religion
	2. Financial	• Afford to provide • Received help
	3. Knowledge and experience	• 'I have knowledge...' • Caring experience
	4. No choice	• Stigma • No one wants to care • Personal status
3. Support from others	1. Close person	• Siblings and relatives • Spouse and children
	2. Significant others	• Maid and friend
4. Environment factor	1. Home	• Convenient house • Distance

physical, mental or psychological health. As a result, many older individuals became dependent on caregivers to continue their daily activities.

Master Theme 1: Personal Factors of the Elderly

Older individuals with illnesses that impair their physical, mental or psychological abilities may require a caregiver to assist them. This is often indicated by changes in behaviour and personality that resemble those of small children, demonstrating the need for additional care from a caregiver. These individuals may lose their ability to function independently, requiring assistance with daily tasks. All the participants in this study were caring for an older person who had an illness, and they observed changes in their loved one's behaviour and capabilities after the diagnosis of a medical condition that had the potential to impact their quality of life.

" ... My husband was diagnosed with Parkinson's disease, and after a few years, he began to experience difficulty urinating. It was sudden and unexpected, and it required immediate medical attention."

" ... My mother has memory problems and often forgets what she has done. For instance, she might forget that she has already eaten or taken a bath, and sometimes she forgets if she has already prayed. Additionally, she has trouble remembering the day and time, which can be challenging for her and those around her."

Realising the limitations caused by illness, many things that the older person is unable to do anymore. Their performance regresses, and they need a lot of help and assistance daily. The moment illness affects older people, they lose the ability to perform daily activities. This is the beginning of dependency on caregivers, especially in managing themselves in daily life, such as feeding, dressing, personal hygiene, and mobility. This situation causes them to need extra care and supervision, especially to maintain their health and safety in every setting.

" ... I had to go up and down to attend follow-up health clinics. Despite the challenge, I made sure to attend all the appointments to ensure proper care and treatment for him."

" ... While taking a shower, we place my father on a seat next to his wheelchair and then carefully wheel him into the bathroom. Once inside, we assist him with the shower and ensure his safety and comfort throughout the process."

The care recipients in this study were dependent on the caregiver in managing themselves. Caregivers needed to help and assist them every day at home, and this became a routine and responsibility for the caregivers.

Master Theme 2: Personal Factors of Caregivers

Caregivers may choose to care for older persons for various reasons. Some may do it out of a sense of financial security, while others may feel they have the knowledge and experience to provide the best possible care. Conversely, some caregivers may feel compelled to provide care despite having no desire to do so. The majority of caregivers in this study chose to care for their elderly loved ones out of a sense of personal motivation. They felt a responsibility to care for the older person given the close relationship they shared, such as parent-child or spouse. The participants in the study were primarily Malays and Muslims, and their religion emphasises the importance of showing devotion to parents. Hence, caregivers in the study saw caregiving as a way to reciprocate the kindness and services provided by their elderly loved ones. The strong bond and relationship between caregiver and care recipient often lead to a sense of duty and responsibility to care for the older person. Religion also plays a significant role in motivating caregivers, instilling an obligation to care for parents. Thus, caregiving can be seen as a way to repay the kindness and services received from elderly loved ones and fulfil religious obligations.

" ... I have always wished to work near Lipis so that I can be close to my parents and take care of them. Being able to support and care for them is a top priority for me."

" ... As children, it's our responsibility to take care of our parents, and it's a driving factor for me. I want to repay my mother for everything she has done for me by taking care of her in her old age. It's a small way of showing my love and gratitude towards her."

Caregivers believe that by caring for the older person, they are being responsible to them and able to repay the care recipients by returning the same actions as previously done by the care recipients.

Financial support could be one of the reasons caregivers are able to provide caregiving. The caregivers in this study can afford to provide caregiving for the older person, and they have no financial issues to support them. This is because the caregivers in this study are mostly employed, which allows them to earn money from their jobs and receive financial support from others in caregiving. The financial support usually comes from close family members.

" ... I feel fortunate that I have a job that enables me to support my mother financially without any difficulties."

" ... We are willing to buy any necessary medical equipment, such as beds, blood pressure monitors, and any required medicines. We also invest in high-quality medical-grade bed pads to ensure comfort and hygiene for our loved ones."

Family caregivers who have good financial support are able to provide the care recipients' essentials and meet their needs for care at home. Some families are able to provide medical equipment for the older person to ensure their comfort when caring at home.

Knowledge and Experience

Interestingly, a few of the caregivers had good knowledge of caring for older people. They gained this knowledge through their experiences at work and previous caregiving experiences, which makes them the most suitable individuals to perform caregiving.

" ... Based on my current job and expertise in healthcare, I believe I am the most suitable person to provide care for my loved ones. Despite having five sisters, I believe the most qualified individuals should take up the responsibility, given their knowledge and skills in terms of care and prevention. Moreover, as the only one residing in Lipis, I feel it's my duty to take care of my loved ones in need."

" ... The experience that taught us about caregiving was not while looking after our father but rather when our aunt took care of our late mother. Her approach and methods provided us with valuable insights and learnings, which we can apply while taking care of our loved ones in the future."

Caregivers believe that with the knowledge and experiences they have, they are capable of managing the health and well-being of the sick and elderly. Most caregivers who have knowledge and caregiving experience apply that knowledge when caring for other older individuals.

No Choice in Caregiving

This concept refers to situations in which caregivers perceive that they have no other option but to provide care for an older person. This may occur when no one else is willing or able to take on the caregiving role. Additionally, social stigma and personal status can play a role, as society often views individuals who refuse to care for the older person negatively. Unmarried or unemployed individuals may be assumed to have fewer commitments, and this perception can influence them to assume caregiving responsibilities despite their own preferences or circumstances.

In some cases, caregivers may feel that they have no choice due to the death of a potential caregiver, leaving them as the only available option. These factors can create a sense of obligation that may affect the quality of care or the caregiver's well-being.

" ... My aunt fell ill, and unfortunately, she passed away. After her demise, there was no one left who was willing to take care of my grandmother in the village."

" ... Sadly, there is nobody who is willing to take care of my grandmother, and we are not keen on sending her to an old folks' home. Despite her age, she still has many other family members who love her and care for her deeply."

Even though caregivers feel they have no choice, they still provide caregiving for the older person. This is because they still feel responsible for the older person, and most of them do not have the intention to put the older person in a nursing home. Hence, they provide caregiving even though they must do it.

Master Theme 3:
Support from Others

Realising that support from others, including close family members and significant others, may help the caregivers in caregiving. The support comes in different ways. Others usually support by providing care assistance for the older person and also moral support. Caregivers receive support from siblings, relatives, husbands, and children. Each of them helps the caregivers when in need, especially when running errands, to ease the caregivers in the caregiving process.

" ... If any of my siblings are unable to provide care, we may seek assistance from our nieces or nephews to help take care of our loved ones."

" ... When I am at work, my husband will take care of my grandmother in our house. He will ensure that she is safe and comfortable while I am away, providing the necessary support and care that she needs."

Significant Others

Caregivers in this study not only receive support from close family members but also from outside individuals such as maids and friends who assist and support them in caregiving. In another view, the help from others actually helps calm the hearts of the caregivers.

" ... When my aunt goes to work, she requires an assistant to manage the tasks efficiently. The assistant must feed and take care of him. If we are busy working during that time, the assistant also needs to handle his urinary and bowel movements."

"Our group comprises supportive and caring friends who always have each other's backs. Whenever any one of us faces a challenging situation, we encourage and uplift each other by saying, 'It's okay, you don't need to worry about it. I'll take care of it. You can focus on other things.' Although these actions may seem small, they significantly reduce our stress levels and help us overcome our challenges with ease."

Colleagues not only help in work but also serve as important people whom caregivers can talk to when needed, especially to share the situation of handling the older person at home. Even though they are not family members, their help is able to reduce the caregiving burden that the caregivers feel.

Master Theme 4:
Environmental Factors
The environment is an important factor when providing caregiving for an older person, especially the home, which is the setting for caregiving. This can help ease their tasks in managing the older person at home. A convenient house that suits the care recipient is important because they live there, while the proximity to facilities and other family houses may be a factor for the caregiver to provide the caregiving. They feel that it is convenient for caregiving.

" ... My house is conveniently located for my mother's care since some of her children reside in the nearby apartment complex. This makes it easier for us to coordinate and provide care for her."

" ... I am grateful that my house is equipped with some disability-friendly features, which make it more accessible for my loved ones who have mobility challenges."

The home environment plays a crucial role in facilitating caregiving for older individuals. A suitable and accessible home environment can significantly contribute to the well-being and comfort of the care recipient, making it easier for caregivers to provide the necessary care and support.

DISCUSSION

The findings of this study shed light on the multifaceted nature of caregiving for older individuals and the factors that influence the caregiving experience. This study revealed four main themes that contribute to caregivers' decision to care for an older person living at home: personal factors of the elderly, personal factors of the caregiver, support from others, and environmental factors. These themes align with previous research that highlights the impact of health conditions and disabilities on the older person, the strong desire of caregivers to care for their loved ones, the sense of responsibility and reciprocity, and the importance of support networks in caregiving.[7,14-16]

The personal factors of the older person, including medical illness and functional limitations, significantly influence the need for caregiving. The study participants observed that the older person often exhibited child-like behaviours and personalities, despite their advanced age and physical decline. This finding echoes the challenges faced by seniors in managing daily tasks and self-care due to long-term illness or disability[4,7]. Caregivers recognised the need to ensure the maintenance of the elderly's self-care and relied on their presence and assistance to fulfil this role. Furthermore, the personal factors of the caregiver played a crucial role in their decision to provide care. The close relationship between caregivers and the care recipient, especially in parent-child dynamics, generated a strong motivation to reciprocate the care received during childhood.[15,16,18] Caregivers felt a sense of responsibility and fulfilment in their role, driven by their desire to give back to their parents.[12,16,20] Religious beliefs also influenced caregiving decisions, with caregivers perceiving their role as an act of obedience and devotion to their faith. The role model of a father who practised religious teachings further reinforced the caregiver's commitment to caring for the older person.[15,20]

Financial stability and the ability to meet the needs of the care recipient emerged as important factors for caregivers. Some caregivers had the financial means to provide daily essentials, healthcare management, and assistance aids, which enhanced the comfort and well-being of the older person. In some cases, caregivers received financial assistance and aid from external sources, supporting their ability to fulfil the caregiving role. The caregivers' knowledge and experience in managing the older person's care also contributed to their confidence and belief that they were qualified for the caregiving task.

However, the study also highlighted situations where caregivers felt compelled to provide care due to limited alternatives. The stigma associated with not providing care and the absence of other available caregivers influenced their decision-making process. In some cases, the death of a previous caregiver or the lack of commitment from other family members necessitated the caregiver to assume the caregiving responsibility.[16,23,24] The marital status of the caregiver also played a role, with single caregivers potentially having fewer responsibilities compared to their married counterparts.[19] Gender also appeared to influence the distribution of caregiving roles, as women were more commonly involved in caring for the elderly.[24]

Caregivers received support from various sources, including siblings, family, spouses, children, maids and friends. The assistance provided by family members and relatives, both in terms of caregiving support and moral encouragement, was vital in facilitating the caregiving process. Even when care was not shared, other family members were often willing to help.[23] Additionally, assistance from maids eased the caregiving burden, particularly for working caregivers. Support from understanding friends or colleagues also played a significant role, providing caregivers with opportunities for conversation, support, and shared experiences.[25]

Lastly, the caregiving experience is significantly influenced by environmental factors. Caregivers identified the importance of a convenient and disability-friendly home environment, as it eased the caregiving tasks and improved the overall quality of care. Accessibility to necessary facilities and proximity to relatives' houses also played a role in facilitating caregiving, providing caregivers with readily available support and assistance when needed.

CONCLUSION

Research findings revealed that caregiving for an older person living at home is bound by the need to provide a holistic care, influenced by a complex interplay of personal, social, and environmental factors. These invaluable insights shed light on the reasons caregivers choose to provide care, emphasising the importance of understanding these factors in developing robust support systems. By acknowledging and addressing the personal, social, and environmental aspects of caregiving, policymakers, healthcare professionals, and society as a whole can better support caregivers in their crucial and deeply compassionate role of caring for the older person.

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ETHICS APPROVAL AND INFORMED CONSENT

This study was approved by the Research Ethics Committee (REC) UiTM. Ref. number: REC/06/2021 (MR/465) and the informed consent was obtained from all the participants.

CONFLICT OF INTEREST

None.

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The clinical and geographical characteristics, health-seeking behaviours of ST-segment elevation myocardial infarction patients with their total ischaemic time and short-term cardiac mortality outcomes: a local geographical perspective from a developing country

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ABSTRACT

Introduction: Ischaemic heart disease including ST-segment elevation myocardial infarction (STEMI) is the leading cause of death among Malaysians. Total ischaemic time (TIT) which consists of patient delay and systemic delay is a strong predictor of cardiovascular outcome in STEMI. Primary percutaneous coronary intervention (PPCI) is superior to medical thrombolysis in improving STEMI patients' survival outcomes. Our study aims to provide an insight into the clinical and geographical characteristics of STEMI patients, their health-seeking behaviour, TIT, interventions received and short-term cardiac mortality outcomes in the effort to improve the existing coronary care service.

Materials and Methods: This is a descriptive study looking into patients who were diagnosed with STEMI and presented to or were referred to Sarawak Heart Centre between 1st July 2022 and 31st December 2022.

Results: A total of 183 patients were recruited and 33.3% were <50 years old. The majority were in a different division during symptom onset from where the local PPCI centre is located and some underwent one or two transits before arrival at the revascularisation centre. More presented out-of-hour and they were more likely to present within the PPCI window. The median TIT for the study population was 3.3 hours. The short-term cardiac mortalities were 9.3% and only the Killip class was found to have a significant association. In this study, TIT was not significantly associated with short-term mortalities but those who died had a longer median TIT.

Conclusion: A local STEMI network should be set up using the 'Hub-and-Spoke' model in a staged-wise approach to reduce TIT given that PPCI is now the gold standard of treatment alongside continuous effort in patient education.

KEYWORDS:
ST-elevation myocardial infarction, total ischaemic time, geographical characteristics, health-seeking behaviours, developing country

INTRODUCTION

Ischaemic heart disease is the leading cause of death among the Malaysian population.[1] ST-segment elevation myocardial infarction (STEMI) among acute coronary syndrome stands the highest in-hospital and 30-day cardiac mortalities at 23.8% and 18.2% respectively in this nation.[2] Earlier revascularisation has been proven to confer better survival outcomes among STEMI patients.[3] The timeliness of revascularisation is measured by the mean of total ischaemic time (TIT) which is defined as the duration from symptom onset of chest pain till revascularisation and is contributed by patient delay and system delay.[4]

Patient delay is defined as the time of symptom onset to first medical contact.[5] It is mainly attributed to patients' awareness of the timeliness of their presentation and the location of patients at symptom onset which are part of the pre-hospital delay and directly affect the symptom-to-door time, and in turn, contribute to TIT. A study showed that pre-hospital delay has a greater impact than door-to-balloon time (DTB) on TIT.[6] System delay, on the other hand, is defined as the time from first medical contact to revascularisation and is contributed by non-patient-related factors including emergency medical service, transfer delay, and intra-hospital delay. TIT is a stronger predictor of cardiovascular outcome and is used to assess the performance of STEMI by the European Society of Cardiology.[4,5,7-9]

There are two modes of revascularisation, including primary percutaneous coronary intervention (PPCI) and fibrinolytic therapy. The timeliness of their administration is termed as DTB and door-to-needle (DTN) time respectively and directly contributes to the system delay of TIT. Fibrinolytic therapy is widely available in most hospitals and can be easily administered by any healthcare personnel. PPCI on the other hand, is technically demanding and can only be performed by a skilled interventional cardiologist in a catheterisation laboratory. Hence, in Malaysia, fibrinolytic therapy is still more widely performed than PPCI and is part of the recommendation by the National Clinical Practice Guideline (CPG) for the management of STEMI taking into account the

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socio-economic status and infrastructure availability of the local settings.[10] However, PPCI has been proven in multiple trials to be superior to medical thrombolysis in improving the survival outcomes of STEMI patients.[11-15]

Developing countries like Malaysia are not spared from the grasp of cardiovascular diseases such as STEMI. Every effort should be taken to improve the PPCI service sustainably for the long-term benefit of the local population given the evidence of its benefit and to strive to improve TIT at every level. While the effort to improve DTN and DTB time should be continued, the importance of pre-hospital healthcare services should not be overlooked. To improve pre-hospital healthcare and to expand the PPCI service, a geographical perspective of the local distribution of STEMI patients is important to evaluate the coverage of existing coronary care services for the revision of future care plans and service expansion. However, no existing data to date is available to show the local geographical distribution of STEMI patients at symptom onset before their admissions to a PCI-capable hospital in Southern Sarawak, Malaysia.

Sarawak Heart Centre, which is our study centre, is the only PCI-capable government hospital within the state of Sarawak and is located in the southern region, catering for approximately 1.2 million population.[16] The focus of the study is therefore, based on the patient's population within the southern region of Sarawak where delivery of PPCI service is possible given the location of the only PCI-capable centre in the state, which aims to provide an insight into the clinical and geographical characteristics of patients, their health-seeking behaviour, TIT, interventions received and short-term cardiac mortality outcomes which consist of in-hospital and 30-day cardiac mortalities among STEMI patients in the region, in tandem with the objective of Global Heart Attack Treatment Initiative (GHATI) to improve STEMI care. GHATI was launched by the American College of Cardiology in 2019 which works to improve heart attack outcomes of acute coronary syndrome (ACS) patients in low- and middle-income countries.[17] Information on the local geographical distribution of STEMI patients at symptom onset will also be provided in this study to establish a STEMI network within the local setting of southern Sarawak and in the hope of the expansion of service to reach out to the whole state in the future.

MATERIALS AND METHODS

Study Design and Setting

This is a descriptive study looking into patients who were diagnosed with STEMI and presented to or were referred to Sarawak Heart Centre between 1st July 2022 and December 2022, to study the characteristics, health-seeking behaviour of patients, TIT, interventions received and short-term cardiac mortality outcomes which consist of in-hospital and 30-day cardiac mortalities. Sarawak is a state of Malaysia located in the region of East Malaysia in northwest Borneo. Historically, the state of Sarawak was divided into five administrative divisions before the current 12 divisions (Betong, Bintulu, Kapit, Kuching, Limbang, Miri, Mukah, Samarahan, Sarikei, Serian, Sibu, Sri Aman) (Figure 1A). Sarawak Heart Centre is located in the Samarahan division in the southern region of Sarawak. When the emergency medical service team from the southern region of Sarawak receives an emergency call for a patient with suspected STEMI, the patient is sent to the nearest government medical centre within the division which is usually a secondary hospital for further evaluation and treatment including administration of fibrinolytic therapy if not for consideration of PPCI, before the decision of referral to a PCI-capable hospital which is our study centre. STEMI patients beyond the southern region of Sarawak will receive fibrinolytic therapy due to the non-availability of PPCI service and will only be referred to Sarawak Heart Centre for elective PCI later. During the acute admission, they are managed at the secondary hospital within their respective divisions.

Sarawak Heart Centre has cardiology and cardiothoracic departments to provide a comprehensive coronary care service. The Cardiology Department consisted of a total of 40 inpatient beds including eight beds in the coronary care unit and 32 beds in cardiac rehabilitation wards to provide high to low dependency inpatient care.[18] Patients who present with acute STEMI were admitted under the cardiology department and later referred for cardiothoracic services should open heart bypass surgery be required.

Participants

All patients from the southern region of Sarawak namely divisions of Kuching, Samarahan, Serian, Sri Aman and Betong who were diagnosed with STEMI and presented to or were referred to Sarawak Heart Centre between the period of 1st July 2022 and 31st December 2022 were recruited. Only patients from these divisions were included because, beyond these, it is not feasible to cover primary PCI service in terms of the travelling time with the current availability of PCI-capable centres in Sarawak.[10] Exclusion criteria include patients who were initially treated for STEMI but were later confirmed to have other diagnoses.

Data Collection and Outcome Measured

Demographic data including patients' age, sex, ethnicity, marital status, and cardiovascular risk factors were collected. In addition, the type of location during symptom onset, duration and distance from symptom onset to first medical contact, duration and distance from first medical contact to revascularisation centre, total distance travelled, DTN, DTB, TIT, Thrombolysis in Myocardial Infarction (TIMI) risk score, Killip score, mode of revascularisation, choice of fibrinolytic agent and revascularisation outcomes were recorded. Duration from symptom onset till arrival at first medical contact was then divided into groups of <3 hours, 3-12 hours, and >12 hours with cut-off values taken from the Malaysia Clinical Practice Guideline (CPG) for acute management of STEMI, 2019 to evaluate the adherence to the guideline for the mode of revascularisation or treatment received. These three groups of patients were also regrouped into ≤12 hours and >12 hours for subsequent analysis. The 12-hour cut-off is the determinant for PPCI.10 TIMI score was categorised into groups of low TIMI risk scores of 0-5, moderate TIMI risk scores of 6-7, and high TIMI risk scores >7. As for Killip classification, Killip I and II were considered as low Killip class whereas Killip III and IV were considered as high Killip class. The outcomes measured were patient delay, TIT, in-hospital and 30-day cardiac mortalities.

Statistical Analysis
Statistical analysis was performed with IBM SPSS version 27. Continuous variables with normal distribution were presented as mean (standard deviation) whereas skewed distributions were presented as median (interquartile range). Others include categorical data with quantitative variables which were presented in frequency (percentage). The Mann-Whitney U test was used for numerical variables and either Pearson's chi-square test or Fisher's exact test was used for categorical variables. Correlations between the total distance travelled from symptom onset till revascularisation and TIT was examined using the Pearson correlation coefficient test. Multivariable logistic regression analysis was used to determine the associations when there was more than one significant variable. Statistical significance was set at p-value <0.05.

Ethics
This study was approved by the Medical Review and Ethics Committee (MREC), Ministry of Health (MOH) in 2023 (Approval code: NMRR ID-23-00747-YFQ). MREC waived the informed consent for this study.

RESULTS

Clinical Characteristics
A total of 183 patients with STEMI were included in this study, amounting to an average of 31 STEMI patients per month in Sarawak Heart Centre. The median age of our study population was 55 years, and they were predominantly male. A vast majority of 175 (95.6%) had at least one cardiovascular risk factor, with smoking being the most common one. Most (75.3%) were at home when chest pain occurred. Hundred and thirty-three (73.5%) had low TIMI categories whereas 146 (80.7%) were Kilip I or II. Other clinical characteristics of patients are stated in Table I.

Geographical Characteristics
The majority of the patients were in the Kuching Division when chest pain occurred, which is a different division from where SHC is located (Figure 1B).

The median distance from symptom onset to the nearest hospital and Sarawak Heart Centre was 7.9 (range 4.1-16.4) km and 19.0 (range 13.8-34.1) km respectively with the maximum distance travelled being 396 km.

Patients' Health-seeking Behaviour and Pattern
Hundred and thirty-three (72.7%) presented to a hospital of whom 32 (17.5%) presented directly to SHC and 115 (63.2%) presented out-of-hour. Further information on the pattern of patient health-seeking behaviours in terms of FMC is available in Table II.

Ninety-four (70.7%) patients received revascularisation therapy at first medical contact . Patients who presented to first medical contact without revascularisation service or were unable to afford the payment of treatment such as those who went to private medical centres, needed to undergo one or two transits. Those who transited once before reaching the revascularisation centre consisted of 37 (27.8%) patients while those who transited twice before receiving revascularisation therapy consisted of two (1.5%) patients.

Those who presented to other non-PCI-capable hospitals were eventually sent to our cardiac centre for post-revascularisation care after receiving fibrinolytic therapy. One hundred and thirty-three (73.1%) patients transited once to another hospital before reaching SHC. Those who transited twice before arrival at SHC consisted of 15 (8.2%) patients.

Total Ischaemic Time and Interventions Received
The median TIT of our study population was 3.3 hours. Those presenting to the government or private clinics had a median TIT of 4.3 (3.1, 6.7) hours, which was significantly longer than those presenting to hospitals who had a median TIT of 2.9 (2.0, 4.9) hours (p=0.005, Z= -2.832). Also, those presenting to non-PCI capable, and PCI capable centres had median TIT of 3.5 (2.3, 5.1) and 2.3 (1.7, 4.6) respectively (p=0.029, Z= -2.187). Those who transited once before reaching a revascularisation centre had a longer median TIT of 4.3 (range 2.9-7.9) hours than those who presented directly to a revascularisation centre with a median TIT of 2.9 (range 2.0-4.6) hours (p=0.004). Those in rural areas at symptom onset had a significantly longer median TIT of 4.1 (range 2.7-6.8) hours than those in urban areas who had a median TIT of 2.9 (range 2.0-4.6) hours (p=0.012, Z= -2.499). Those who were at home and out of home at symptom onset had median TIT of 3.9 (range 2.1-5.7) hours and 2.8 (range 2.2-3.9) hours respectively (p=0.026, Z= -2.219).

Among our study population, 60.1% received fibrinolytic therapy and 12.0% received PPCI. Hundreds and two (77.3%) adhered to CPG for the mode of revascularisation. The median DTN and DTB times were 37 minutes and 55 minutes respectively.

Of those who received PPCI, those who presented directly to SHC had a shorter median TIT of 2.9 hours than those who presented to other non-PCI-capable hospitals in which the median TIT was 4.2 hours. Even for those who received fibrinolytic therapy, the TIT was shorter for those who presented directly to the study centre than those who presented to other centres (Figure 2).

Of the 52 (28.6%) patients who received medical therapy, 37 (71.2%) were due to late presentation myocardial infarction, 11 (21.2%) experienced spontaneous resolution of ST-segment elevation from 12-lead electrocardiogram and symptom relief before revascularisation, 1 (1.9%) refused thrombolysis therapy and 3 (5.8%) died before any revascularisation was given. Three (2.3%) patients underwent rescue PCI due to failed thrombolysis from fibrinolytic therapy.

There was no correlation between the total distance travelled from symptom onset to the revascularisation centre and TIT (R^2=0.020).

Patient Delay and the Associated Factors
Hundreds and fifty-seven (86.7%) patients presented for medical attention within 12 hours or less and were within the PPCI window. Of the late presenters who presented beyond 12 hours, two (8.3%) had a history of ischaemic heart disease

Table I: Characteristics of patients with myocardial infarction and survival outcomes

Characteristics	n(%)	(min, max)
Age in years - median (IQR)	55.0 (47.0, 66.0)	25.0, 82.0
Age <50-year-old	61 (33.3)	
Age ≥50-year-old	122 (66.7)	
Sex		
Male	160 (87.4)	
Female	92 (12.6)	
Ethnicity		
Malay	76 (41.5)	
Chinese	44 (24.0)	
Indian	1 (0.5)	
Indigenous	60 (32.8)	
Foreigner	2 (1.1)	
Marital status		
Married	151 (83.9)	
Single	12 (6.7)	
Divorced	11 (6.1)	
Widowed	6 (3.3)	
Risk factors		
No	8 (4.4)	
One	51 (27.9)	
Two or more	124 (67.7)	
Hypertension	87 (47.5)	
Diabetes mellitus	46 (25.1)	
Dyslipidaemia	67 (36.6)	
Family history of IHD	37 (20.6)	
Personal history of previous IHD	18 (9.8)	
Smoking	118 (65.2)	
Regular alcohol use	41 (22.9)	
Location during symptom onset		
Home	137 (75.3)	
Workplace	14 (7.7)	
Non-home, non-workplace	31 (17.0)	
Time of presentation at FMC		
Office hours	67 (37.0)	
Out of hours	115 (63.2)	
Type of healthcare facility upon presentation		
Government or private clinic	50 (27.3)	
Hospital	133 (72.7)	
PCI capable centre	33 (18.0)	
Non-PCI capable centre	150 (82.0)	
Duration from symptom onset to FMC in hours- median (IQR)	2.3 (1.2, 5.2)	0.2, 150.5
Duration of symptom onset to FMC		
<3 hours	114 (63.0)	
3 -12 hours	43 (23.8)	
>12 hours	24 (13.3)	
Duration from FMC to revascularisation centre in hours- median (IQR)	1.8 (1.3, 2.4)	0.7, 4.5
Mode of revascularisation		
PPCI	22 (12.0)	
Fibrinolytic therapy	110 (60.1)	
Medical therapy*	51 (27.9)	
Adherence to CPG recommendation for mode of revascularisation	123 (68.0)	
Choice of fibrinolytic agent		
Tenecteplase	18 (16.4)	
Streptokinase	92 (83.6)	
Door-to-needle time in minutes - median (IQR)	37.0 (22.0, 76.0)	
Door-to-needle time in minutes ≤ 30 minutes	41 (38.3)	
Door-to-balloon time in minutes - median (IQR)	55.5 (49.8, 77.3)	41.0, 184.0
Door-to-balloon time in minutes ≤ 90 minutes if presented to PCI capable centre or ≤ 120 minutes from FMC to wire-crossing if transferred from non-PCI capable centres	19 (86.4)	
Revascularisation outcome		
Successful	129 (97.7)	
Failed	3 (2.3)	
Rescue PCI	3 (2.8)	
Total ischaemic time in hours- median (IQR)	3.3 (2.1, 5.0)	0.5,55.1

Table I: Characteristics of patients with myocardial infarction and survival outcomes

Characteristics	n(%)	(min, max)
Total distance travelled between symptom onset and revascularisation centre in kilometres - median (IQR)	12.1 (7.6, 23.4)	0.8, 109.7
TIMI score- median (IQR)	3.0 (2.0, 6.0)	0.0,12.0
TIMI categories		
Low TIMI risk score	133 (73.5)	
Moderate to high TIMI risk score	48 (26.5)	
Killip score- median (IQR)	1.0 (1.0, 2.0)	1.0,4.0
Killip categories		
Killip I-II	146 (80.7)	
Killip III-IV	35 (19.3)	
In-hospital cardiac mortality outcome		
Alive	166 (90.7)	
Dead	17 (9.3)	
30-day cardiac mortality outcome		
Alive	166 (90.7)	
Dead	17 (9.3)	

CPG: Clinical practice guideline, FMC: First medical contact, IHD: Ischaemic heart disease, km: Kilometre, PPCI: Primary percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction.
*Refer to standard acute coronary syndrome treatment (high-dose acetylsalicylic acid, high-dose P2Y12 inhibitor, fondaparinux/enoxaparin and high-dose statin)

Table II: Pattern of patient health-seeking behaviour according to FMC in different locations and the treatments received

		First medical contact				
		Hospital (n=133)			Clinic (n=50)	
		Government (n=115)		Private (n=18)	Health clinic (n=26)	General practitioner (n=24)
		PCI centre (n=32)	Non-PCI centre (n=83)			
Nearest medical centre*	Government	24	42	3	16	11
	private	7	38	15	10	12
	PCI centre	23	4	1	9	6
	Non-PCI centre	8	76	17	17	17
Location of symptom onset	Urban	25	51	18	13	18
	Rural	6	31	0	13	6
Time of presentation	Office hour	10	22	5	18	12
	Out of hour	22	60	13	8	12
Treatment received	PPCI	9	1	3	8	1
	Fibrinolytic therapy	15	66	9	11	9
	Medical therapy	8	16	6	7	14
Districts	Kuching	12	52	17	13	16
	Bau	-	5	-	-	1
	Lundu	-	6	-	-	-
	Samarahan	17	1	1	2	6
	Asajaya	1	-	-	4	-
	Simunjan	-	1	-	-	-
	Sebuyau	-	-	-	3	-
	Serian	-	12	-	1	1
	Siburan	1	-	-	1	-
	Tebedu	-	1	-	-	-

*Nearest medical centre is the nearest centre from the patient at symptom onset according to the distance calculated but is not necessarily the centre of presentation or FMC.

Table III: Factors associated with duration from symptom onset to arrival at FMC were analysed using Pearson's chi-square test

Factors	Duration from symptom onset to arrival at FMC		χ^2 (df)	p-value
	≤12 hours n (%)	>12 hours n (%)		
Age				
<50 years	52 (86.7)	8 (13.3)	0.000	0.984
≥50 years	105 (86.8)	16 (13.2)		
Gender				
Male	135 (85.4)	23 (14.6)	1.819	0.177
Female	22 (95.7)	1 (4.3)		
Ethnics				
Malay	63 (84.0)	12 (16.0)	1.444	0.837
Chinese	38 (86.4)	6 (13.6)		
Indian	1 (100.0)	0 (0.0)		
Indigenous	53 (89.8)	6 (10.2)		
Foreigner	2 (100.0)	0 (0.0)		
Marital status				
Married	128 (85.9)	21 (14.1)	0.293	0.589
Single/divorced/widowed	26 (89.7)	3 (10.3)		
Number of risk factors				
Less than 2	54 (93.3)	4 (6.9)	3.005	0.083
Two or more	103 (83.7)	20 (16.3)		
Smoker				
Yes	100 (86.2)	16 (13.8)	0.042	0.837
No	55 (87.3)	8 (12.7)		
Alcohol				
Yes	34 (82.9)	7 (17.1)	0.562	0.453
No	119 (87.5)	17 (12.5)		
Family history of IHD				
Yes	29 (80.6)	7 (19.4)	1.375	0.241
No	125 (88.0)	17 (12.0)		
Hypertension				
Yes	74 (86.0)	12 (14.0)	0.069	0.793
No	83 (87.4)	12 (12.6)		
Diabetes mellitus				
Yes	39 (86.7)	6 (13.3)	0.000	0.987
No	118 (86.8)	18 (13.2)		
Dyslipidaemia				
Yes	56 (83.6)	11 (16.4)	0.923	0.337
No	101 (88.6)	13 (11.4)		
Personal history of IHD				
Yes	16 (88.9)	2 (11.1)	0.080	0.777
No	141 (86.5)	22 (13.5)		
Location of symptom onset				
Home	114 (84.4)	21 (15.6)	2.308	0.129
Out of home	42 (93.3)	3 (6.7)		
Area of symptom onset				
Urban	108 (87.1)	16 (12.9)	0.089	0.766
Rural	47 (85.5)	8 (14.5)		
Time of presentation				
Office hours	51 (76.1)	16 (23.9)	10.433	0.001
Out of hours	106 (93.0)	8 (7.0)		

FMC: first medical contact. IHD: ischaemic heart disease

before the current presentation. Fourteen (58.3%) were within a radius of 20 km from the PCI-capable centre at symptom onset in which there is a disproportionate delay in presentation considering their distance from the treatment centre.

The association of all the factors listed in Table III with patient delay were studied. We found that only the time of presentation was significant in the association. When looking into this factor, the 115 (63.2%) of our study cohort who presented out of hour (Table I) were found to be more likely to present within the golden hour of the PPCI window of 12 hours or less (Odds Ratio, OR: 4.2; 95% Confidence Intervals, 95%CI: 1.7, 10.3) (Table III).

The association between distance and duration from symptom onset to arrival at first medical contact was not significant (p=0.901).

Mortality Outcomes and the Associated Factors

The in-hospital and 30-day (short-term) cardiac mortalities for our study population were 9.3%.

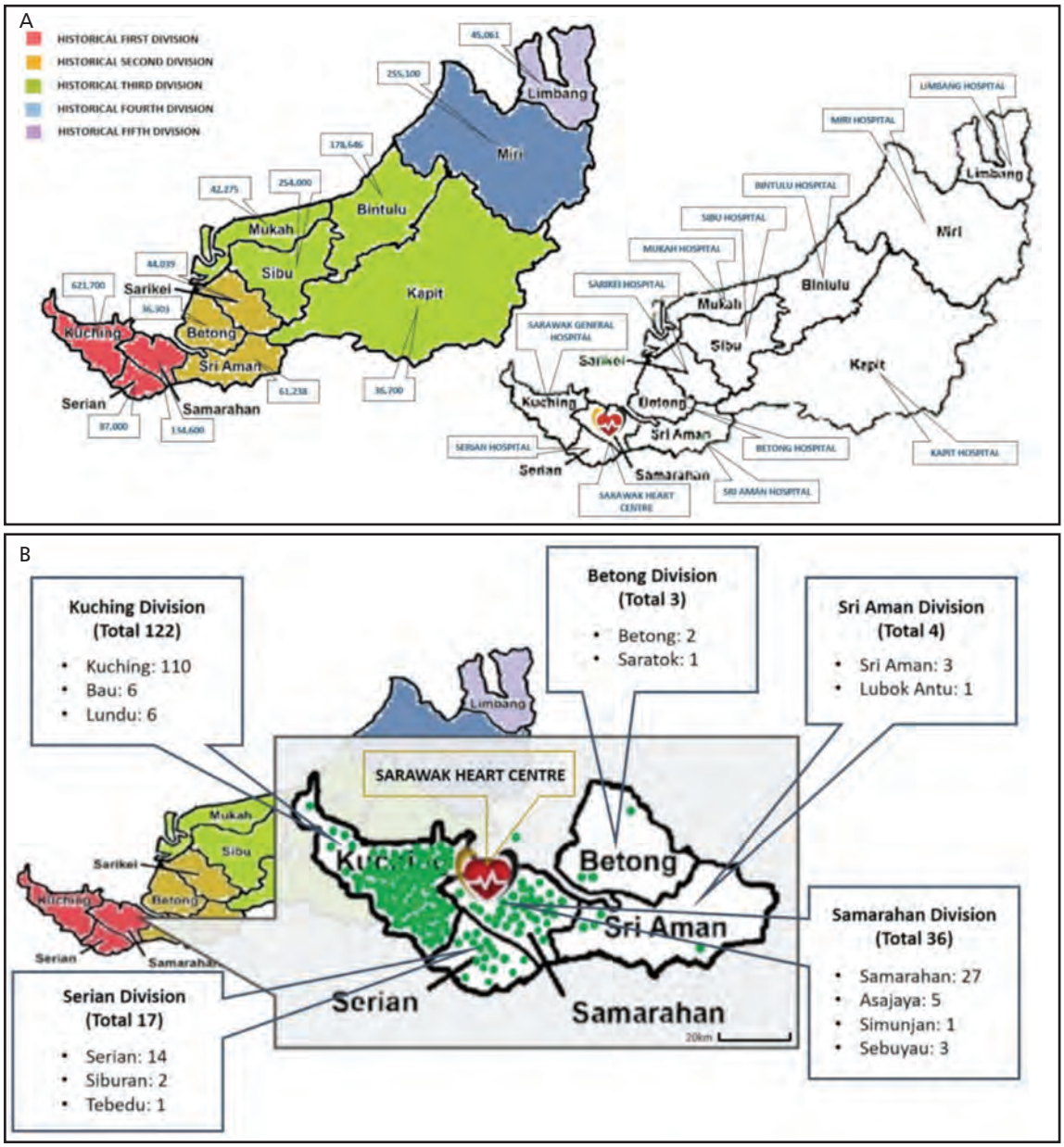


Fig. 1: A) Historical and current administrative divisions of the state of Sarawak, Malaysia and its respective population; B) Geotagging of study population at symptom onset

Univariate analysis using Pearson's Chi-square found that three out of 25 variables from our study were significantly associated with short-term mortalities, namely DTB (p=0.035), TIMI risk score (p<0.001) and Killip class (p<0.001). TIT, was, however, not significant in its association with the short-term mortalities for this study cohort. Nevertheless, those who died had a longer median TIT of 4.3 (range 2.4-8.4) hours than those who were alive with a median TIT of 3.1 (range 2.0-4.8) hours, albeit the association did not achieve statistical significance (p=0.175). The total distance travelled, and the number of transits was also not shown to be associated with mortality outcomes.

When confounding was adjusted using multivariable logistic regression, only the Killip class had a significant association with short-term mortality outcomes (OR 17.2, 95%CI 3.3, 88.5).

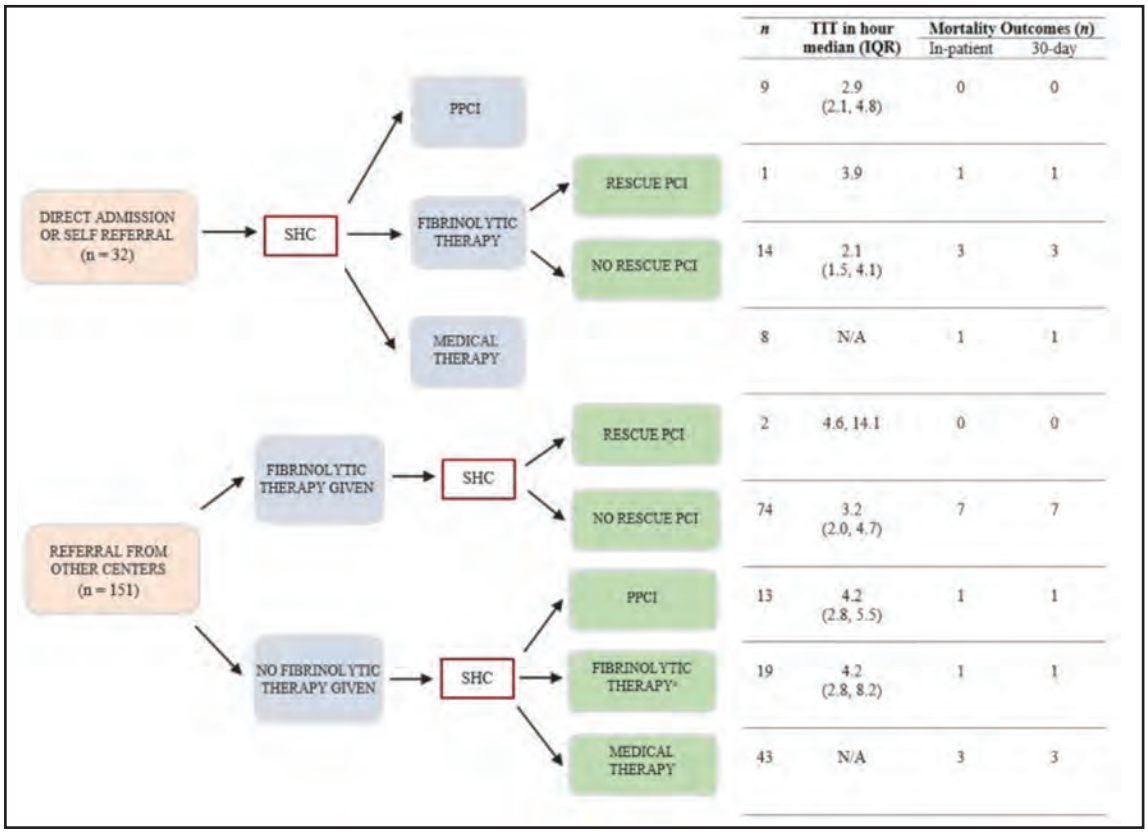
DISCUSSION

Overview

All STEMI patients deserve every effort to improve coronary care services especially when the population in our study consists of relatively young patients. The design of a seamless healthcare system that could shorten the TIT by targeting patient delay and systemic delay is the way forward.

Clinical Characteristics

The demographic trend of our study cohort gives an important insight into our target population for the effective



n	TIT in hour median (IQR)	Mortality Outcomes (*n*)	
		In-patient	30-day
9	2.9 (2.1, 4.8)	0	0
1	3.9	1	1
14	2.1 (1.5, 4.1)	3	3
8	N/A	1	1
2	4.6, 14.1	0	0
74	3.2 (2.0, 4.7)	7	7
13	4.2 (2.8, 5.5)	1	1
19	4.2 (2.8, 8.2)	1	1
43	N/A	3	3

Fig. 2: Flow diagram showing the different methods of presentation with treatment received and mortality outcomes
[a]No rescue PCI performed for patients who received fibrinolytic therapy among those who were referred from other centres.
Abbreviations: N/A = not applicable, PCI = percutaneous coronary intervention, PPCI = primary percutaneous coronary intervention, SHC = Sarawak Heart Centre

delivery of service and treatment. It is worthwhile noting that the percentage of patients among our study cohort who developed STEMI at <50 years old was 33.3% with the youngest being 25 years old. The STEMI population in our study was comparatively younger than the national statistics (55.6 years vs. 56.2 years respectively) as well as the regional Asia-Pacific population (61.6 years).[2,19] The younger trend phenomenon among STEMI patients was also observed in another study cohort.[20] The significant number of STEMI in the younger productive age group is worrying as it can impact the economic growth of the country as well as cause financial burden and stress to the patients and families. This finding is in tandem with a study done in a local population in Klang Valley which showed cardiovascular diseases being the most significant natural cause of sudden cardiac death with similar observation found among young adult population.[21] Classical cardiovascular risk factors are present among STEMI in young on top of a family history of ischaemic heart disease, smoking and male gender.[22-24] This highlights the need for more vigorous effort to improve our coronary care service.

Patient Delay

The median TIT of our study population (198 minutes) was shorter than that of the national level (252 minutes) as well as the TIT in a European country (387 minutes) and another country in Asia (245 minutes).[5,25,26] Nevertheless, there is still a need for further improvement. It can be seen from our study that patient delay is mainly contributed by patient health-seeking behaviour patterns which stemmed from their awareness of timeliness of presentation, the importance of early presentation, and presentation to the correct first medical contact when experiencing the symptoms of chest pain.

From our study, it can be seen that the TIT is not directly proportionate to the distance needed to travel from symptom onset. Patients who live close to the PCI-capable centre might have significant delays in their presentation, resulting in them missing the PPCI window. Although the exact factor that caused the disproportionate delay has not been investigated in this study, it reflected the inadequacy of patients' awareness of the importance of early presentation and the golden hour for PPCI. Patients' awareness translating into time of presentation was best seen in the group of patients who had a previous history of ischaemic heart disease in which they were more likely to present within the PPCI window than those who only experienced the symptom for the first time. Patients who had previous similar history might have been educated from previous admission and hence were better informed on early presentation. The poor level of healthcare awareness among the local general public especially among the rural population was also reflected in a cross-sectional survey for stroke symptoms and risk factors recognition.[27] Many nationwide surveys among Asian countries including Korea, Japan, Singapore and Malaysia

resonated with similar observations in terms of the current gap in coronary care at the pre-hospital level in regard to public awareness.[28-32] While a secondary prevention level of education is important, the general public needs to be aware of the need for early presentation and symptoms suggestive of ACS as primary prevention is still the key to better healthcare.

While 'time is essence' in patients' presentation, patients' education on the right place to present is also another vital component in reducing delay that directly contributes to TIT by reducing unnecessary transits. The general public needs to be aware of the nearest medical centres that provide revascularisation services and to have financial consideration in mind when deciding between a government and a private sector healthcare facility. Information on revascularisation centres should be made widely available to the public on easily accessible websites or patients' information leaflets as part of the primary prevention education during their attendance at regular primary healthcare clinics before the occurrence of cardiovascular events. Multimedia such as television or various social media platforms should be utilised to promote patients' awareness and to empower the general public on knowledge of symptom recognition and steps to be taken should themselves, family members or anyone close by develop symptoms suggestive of ACS.

The majority of our study cohort presented out-of-hour. Of those, they were more likely to present within the PPCI window. However, the availability of PPCI only within office hours caused the majority of them to receive fibrinolytic therapy instead.

Systemic Delay

The foundation of designing a good healthcare system lies in recognising factors that contribute to systemic delay be it at the pre-hospital level or the intra-hospital level. Established regional protocols that are agreeable among different healthcare facilities within the local region can reduce unnecessary systemic delay.

It can be seen from our study that the main density of STEMI patients at symptom onset was from another division, particularly at a nearby division of Kuching. One hundred and eight (59.0%) of our study cohort who were from other divisions out of Samarahan were not sent directly to SHC for PPCI although it was within the revascularisation window and the reach of PCI-capable hospital was within 2 hours. During the activation of the ambulances, patients were sent to a non-PCI-capable hospital within the division of the emergency medical service for arrangement of transfer to Sarawak Heart Centre. This has led to pre-hospital delays that contributed to prolonged TIT.

Although distance is an important consideration when planning for the coronary care service, our study showed that the distance does not preclude patients from presenting within the PPCI window. Hence, the establishment of a STEMI network could potentially further shorten systemic delay and the reduction of the TIT will improve patients' outcomes. Successful examples of STEMI networks can be seen in other Asian countries such as Korea, Singapore and Japan as well as the local regional MySTEMI Network in Malaysia.[33]

Mortality Outcomes

In our study population, the in-hospital mortality was comparable to the national and Singapore data (9.3 vs. 10.3%) but was higher as compared to other Asia-Pacific countries like Australia, Japan and Korea (5.6-5.7%), whereas 30-day mortality was lower compared to national and Singapore statistics (9.3% vs. 12.1%, and 10.4% respectively) but was higher as compared to Australia and Korea (5.9-6.3%)[10,19].

STEMI Network and Suggestions for Improvement

A study in Australia on the system of field triage of STEMI patients by electrocardiogram (ECG)-equipped ambulances and direct catheterisation laboratory transfer found that this system was associated with shorter treatment time and improved survival.[34] Similar field triage has been assimilated into the MySTEMI Network in Klang Valley. MySTEMI network is a local effort in the Klang Valley region of Malaysia to set up a network adapting the hub-and-spoke model to provide better access to immediate care for STEMI patients.[35] They are important reference works to set up a STEMI network in the local region of Southern Sarawak.

Special coronary care ambulances equipped with ECG machines and trained paramedics which are allowed to bypass the non-PCI-capable hospitals are needed for direct transfer with the collaboration of the emergency department and PCI-capable hospital. The ambulance paramedics should be trained to perform a 12-lead ECG on suspected MI patients and for ECG interpretation. ECG showing STEMI can then be transmitted to the emergency department for confirmation and activation of the catheterisation laboratory. Patients can then be transferred directly to the catheterisation laboratory for PPCI if the estimated transfer time is within 2 hours. The ambulances should also be equipped with fibrinolytic therapy for earlier revascularisation for patients who are located further away from the catheterisation laboratory in which the estimated transfer time is more than 2 hours. Electronic communication platforms can be set up to ease the communication between the ambulance paramedics, emergency department personnel and cardiology team.[36]

Similar suggestions were resounded by another study in which the study also promoted integrated care pathways that allow the application of guidelines according to local culture and hospital system which has been shown to reduce the DTB time. Several countries including Korea, Hong Kong and Pakistan have replicated the effort and found the beneficiary effect of the care pathways.[37]

Catheterisation laboratory that operates 24 hours will be able to cater for the needs of more STEMI patients. PPCI service that expands beyond office hours will be beneficiary to the majority of our study cohort who presented out-of-hour. With PPCI now being the gold standard of treatment for STEMI patients, every effort to pursue the delivery of the best possible care should be encouraged.[38-40]

Post-revascularisation care is another part of coronary care service that needs attention. Being the only heart centre in the state within the government setting, Sarawak Heart Centre has only limited beds to cater for all cardiac patients from the whole state of Sarawak. To avoid overwhelming a single centre, a suggestion would be to divert post-revascularised patients from other divisions to other hospitals equipped with intensive care units. Regular updates of patients' progress to the cardiology team through the platform of telemedicine within the local STEMI network can be useful. Using the 'Hub-and-Spoke' model, Sarawak Heart Centre can function as the 'Hub centre' while other hospitals within the network could be the 'spoke hospitals.[16]

The ultimate aim of the STEMI network is to have more cathetherisation laboratories throughout the whole state. With finite resources being the main limitation, a staged approach will be a wise step forward to allow for a gradual and sustainable expansion of coronary care services.

LIMITATIONS AND SUGGESTIONS FOR FUTURE STUDIES

The main limitation of our study is in its single-centre design. With Sawarak Heart Centre being the only patient catchment area, other patients who presented to and then died in other non-PCI-capable centres or private hospitals were not included. This might lead to an under-representation of the mortality rate among the regional STEMI patients. In addition, the small sample size might affect the accuracy of the result. Another limitation is the lack of long-term cardiac mortality and morbidity outcomes within the study cohort. There was also no data regarding patients who relied on the ambulance service for presentation to the PCI-capable centre. This information will be useful to support the need for special coronary care ambulances within the chain of the STEMI network.

Future studies can be done to look into factors that contributed to systemic delay including transit time, transfer delay and the use of ambulance service. Collaborative work from different centres to further evaluate other components of systemic delay can aid in the improvement of coronary care service by focusing on the specific components. A longer follow-up to look into long-term mortality, morbidity and functional outcomes of the study cohort is called for to provide insight into the long-term outcomes. Further patients' characteristics such as cholesterol profile, body mass index, and waist circumference as a comprehensive risk factor can also be investigated as compared to individual cardiovascular risk factors for their association with survival or morbidity outcomes.

CONCLUSION

This study postulates the long-term goal for coronary care services of reducing total ischaemic time (TIT) among ST-segment elevation myocardial infarction (STEMI) patients by overcoming factors that contributed to patient delay and systemic delay including increasing patient awareness through public education and setting up a local STEMI network. Although TIT was not found to have a statistically significant association with short-term mortality outcomes among our study cohort, its significance in long-term survival outcomes of STEMI patients had been well-proven in many studies that its importance should not be ignored with the consideration that primary percutaneous coronary intervention (PPCI) is now the gold standard of treatment for STEMI. The 'Hub-and-Spoke' model can be adopted in setting up a local STEMI network in a staged-wise approach to shorten the pre-hospital and intra-hospital delay in the effort of reducing TIT.

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CONFLICTS OF INTEREST

All authors of this study have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Health-related quality of life and its relationship with time use, role participation and perceived social support among retirees in Klang Valley and Malacca

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ABSTRACT

Introduction: With increased life expectancy among older adults in Malaysia, there is an increasing number of years of living after retirement. The role and lifestyle changes can significantly affect time use and participation in everyday life, influencing individuals' quality of life (QoL) and well-being. However, limited research has examined the health-related QoL and its relationship with time use, role participation and perceived social support among retirees in Malaysia.

Materials and Methods: In this cross-sectional study, we used the Malay versions of EuroQol 5 Dimensional (EQ-5D-3L, Time Use Diary, Role Checklist Version 3 (RCv3) and Multidimensional Scale of Perceived Social Support (MSPSS) questionnaires among 362 purposively selected Malaysian retirees aged 55 and older. Regression analysis was employed to identify the predictor of health-related QoL using the Statistical Package for Social Sciences (SPSS) version 26.

Results: The results indicate a weak positive association between all determinants (time use, role participation, perceived social support) and health-related QoL among retirees. Only time use and role participation significantly influenced the health-related QoL of retirees. Our findings reveal no direct and substantial relationship between perceived social support and health-related QoL among Malaysian retirees.

Conclusion: The results suggest active role involvement and effective time management can improve retirees' health-related QoL.

KEYWORDS:
QoL; retiree; role participation; social support; time use

INTRODUCTION

Malaysia is experiencing an ageing population, with older adults increasing yearly.[1] This trend is attributed to increased life expectancy, driven by advancements in medical care, hygiene and food supply.[2] As life expectancy for older adults increases, the number of years spent living after retirement also increases, leading to changes in responsibilities and lifestyles. As a result, the proportion of adults aged 65 years and above is growing yearly, with the latest figures in 2020 revealing that the senior age population has risen to 7%.[1]

QoL is an individual's perception of their place in life regarding their objectives, aspirations, and standards in the context of their culture and value systems.[3] Numerous standardised measures have been developed to assess QoL, including EQ-5D-3L, and demonstrate its significance in an individual's life. A study has found that health, family and income were among the most influential contributors to QoL.[4] Specifically, almost all older adults emphasised that health significantly contributes to QoL[4], underscoring the importance of health-related QoL.

Moreover, family members, including partners and children, were also highlighted as essential contributors, implying the importance of social support. More than half of the older adults stated health as their top priority, followed by needing children and partners to improve their QoL.[4] Contrarily, despite being emphasised as one of the contributors, income was not among the top priorities contributing to QoL.[4]

Besides QoL, retirement affects many aspects of an individual's life, including role shifts from worker to retiree and routine changes, which may impact QoL.[5,6] Post-retirement, individuals may face limited access to activities, limiting their role engagement and affecting their well-being.[5] Moreover, a slower daily rhythm and changed significance of activities led to a shift towards less demanding and unproductive activities,[5] which may influence QoL. Besides, the absence of daily demands can be stressful and reduce motivation, further impacting QoL.[6] In summary, the retirement experience is closely tied to engaging activities and roles, with the need for a flexible approach to address new themes in activities' transition, such as a new temporal structure and changes in the meaning of activities.

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Despite that, there is a lack of studies in the literature focusing on whether time usage, role engagement and social support impact health-related QoL among retirees. Meanwhile, numerous studies have examined factors associated with QoL in the general elderly population,[7-10] and few have comprehensively evaluated the factors connected to retirees' health-related QoL, particularly in Malaysia. Thus, this study addresses this gap by examining relationships between health-related QoL, time use, role participation and perceived social support among Malaysian retirees, specifically in the Klang Valley and Malacca regions, with an estimated population density of 585-8235 per km^2.[2,11]

MATERIALS AND METHODS

Study Design

A cross-sectional research design was selected to assess the prevalence of a problem and examine the relationships between variables by sampling a representative cross-section of the population.[12] This design is also the most economical and efficient for data collection within the 2-year time frame of the study (March 2021-March 2022).

An online questionnaire was used to collect the data, using the Qualtrics Online Survey platform due to its cost-effectiveness, simplicity, and efficiency in data collection and analysis. Additionally, the data were collected during the fluctuating movement control order due to the progression of the COVID-19 pandemic, where generally physical distancing is enforced, and face-to-face data collection is not allowed but with specific restrictions on different phases of movement control order, location and aspects of life.[13]

Research Ethics Committee granted ethical clearance for this study, reference no: [REC/12/2020 (MR/4360)]. Participation in the study was voluntary, and retirees had complete autonomy in deciding whether to participate. All data from retirees were obtained with informed consent, awareness and explicit permission.

Sampling Method

The study recruited retirees aged 55 and above through purposive sampling. Participants were recruited from the non-governmental organisation Kelab Guru Bersara (Teachers' Retiree Association) and Pusat Aktiviti Warga Emas (PAWE) in the Klang Valley and Malacca regions. Inclusion criteria for participants included living in the community, being able to read and communicate in Malay to complete the questionnaires, and not having any chronic illness that affects their physical, cognitive and psychological function. In addition, exclusion criteria included foreigners who retired in Malaysia as a second home or those who opted for early retirement.

Research Instruments

Four instruments were used to collect participants' data and retirees' socio-demographic details. All instruments have been validated in Malay and have adequate psychometric properties. First, the time use diary is a self-report instrument that captures how retirees use their time over 24 hours.[14] The retirees were required to document their key activities, even if they just spent minutes on them. The instrument's internal consistency was assessed in three areas: main activity, the purpose of the activity and secondary activity, with Cronbach alpha coefficients ranging from 0.02 to 0.85 for the main activity, 0.34 to 0.73 for the purpose and 0.19 to 0.84 for the secondary activity.[15] Besides, known group validity was established by comparing participants over 50 from the community and nursing homes, revealing significant differences in the purpose of activities and time spent with family and at an organisation.[15]

Second, the Role Checklist Version 3 (RcV3) is a brief screening instrument that examines the retirees' involvement levels, satisfaction with participation, and reasons for non-participation.[16] It is a 10-item screening tool that allows clinicians and researchers to provide a client-centred care plan and collect outcome data on an individual or population level. The Role Checklist—Malay demonstrated high content and face validity indices (0.95-0.98 and 0.92-0.96, respectively), good to excellent test-retest reliability (intraclass correlation coefficients: 0.654-0.976), and moderate to perfect agreement (Cohen's kappa: 0.620-1.00).[17] Additionally, the total number of roles was positively correlated with the SWLS – Malay (r_s = 0.593, p<0.001), EQ-5D-3L–Malay (r_s = 0.366, p<0.001), and MSPSS – Malay (r_s = 0.314, p<0.001).[17]

Third, the Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item instrument designed to assess retirees' perceived social support using a seven-point Likert scale ranging from 1 (very strongly disagree) to 7 (very strongly agree).[18] The sum of all 12 elements must be divided by 12 to get a mean score with a range of 1 to 7; a high score indicates high social support. The Malay version of the MSPSS (MSPSS-M) has strong internal consistency, with total scores ranging from α = 0.88 to 0.92 and subscale scores (friends, family, significant others) ranging from α = 0.82 to 0.96 (19-21). It also demonstrates excellent parallel form reliability (rs = 0.94, p<0.001) and test-retest reliability (rs = 0.77, p<0.001).[19] Furthermore, MSPSS-M shows significant correlations with other measures of social support, mental health, and psychological well-being (rs = -0.25 to 0.61, p<0.05 to 0.001).[20,21]

Finally, the EuroQol 5 Dimensional (EQ-5D-3L) is a brief, self-administered instrument of health-related QoL reported by the person (HRQoL). "3L" represents three scale options: no difficulties, moderate problems, and severe problems.[22] This instrument comprises a descriptive system with five domains, including "mobility, self-care, usual activities, pain or discomfort, and anxiety or depression," each rated on three levels of severity: (i) no problem, (ii) some problem and (iii) severe problem. Moreover, the Malay EQ-5D-3L has been validated for semantic, theoretical and linguistic equivalence to the English version.[23]

Data Analysis

Data for this study were analysed using the Statistical Package for Social Science version 25.0 software (SPSS-25). First, the characteristics of the sample were described using descriptive statistics. Next, regression analysis was used to identify the significant predictors of health-related QoL.

Table I: Demographic characteristics of retirees, their QoL, time use, role participation and perceived social support (n=362)

Demographic characteristics	n (%)	Mean (SD)
Age		66.94 (5.43)
Gender		
Female	181 (50.00)	
Male	181 (50.00)	
Religion		
Islam	224 (61.90)	
Christian	40 (11.00)	
Hindu	49 (13.50)	
Buddha	46 (12.70)	
Others	3 (0.80)	
Ethnicity		
Malay	220 (60.80)	
Chinese	74 (20.40)	
Indian	57 (15.70)	
Bumiputera Sabah	7 (1.90)	
Bumiputera Sarawak	2 (0.60)	
Others	2 (0.60)	
Marital status		
Single	10 (2.80)	
Married	289 (79.80)	
Divorced/widowed	63 (17.40)	
Education level		
No formal education	9 (2.50)	
Primary education	40 (11.00)	
Secondary education	122 (33.70)	
Tertiary education	191 (52.80)	
Location		
Urban	275 (76.00)	
Rural	87 (24.00)	
QoL (EQ-5D-3L)		
EQ Overall		74.97 (14.31)
Mobility		
No problem	274 (75.70)	
Some problem	88 (24.30)	
Self-care		
No problem	344 (95.00)	
Some problem	16 (4.400)	
Extreme problem	2 (0.60)	
Usual activities		
No problem	295 (81.50)	
Some problem	61 (16.90)	
Extreme problem	6 (1.70)	
Pain or discomfort		
No problem	203 (56.10)	
Some problem	155 (42.80)	
Extreme problem	4 (1.10)	
Anxiety or depression		
No problem	316 (87.30)	
Some problem	42 (11.60)	
Extreme problem	4 (1.10)	
Time use (hours)		
ADL		3.65 (1.67)
IADL		5.42 (3.40)
Productivity		0.58 (1.45)
Rest and sleep		10.42 (2.98)
Leisure		4.05 (2.63)
Alone		8.03 (7.28)
With family		13.91 (7.53)
With friends		0.94 (1.73)
With spiritual members		1.07 (1.80)
Role participation		
Student	58 (16.00)	
Worker	61 (16.90)	
Volunteer	99 (27.30)	
Care	207 (57.20)	

Table I: Demographic characteristics of retirees, their QoL, time use, role participation and perceived social support (n=362)

Demographic characteristics	n (%)	Mean (SD)
Homemaker	309 (85.40)	
Friend	263 (72.70)	
Family member	335 (92.50)	
Religious participant	294 (81.20)	
Hobby	189 (52.20)	
Organisation	106 (29.30)	
Total number of roles		5.31 (2.20)
Perceived social support		
Significant other		20.91 (4.48)
Family		21.17 (3.32)
Friends		19.99 (3.93)
Total		62.07 (9.96)

Table II: Predictors of QoL among retirees

Model		Unstandardised Coefficients		Standardised Coefficients	t	Sig.
		B	Std. Error	β		
1	(Constant)	51.298	5.505		9.319	<0.001
	Role participation	0.679	0.149	0.243	4.553	<0.001
	Perceived social support	0.014	0.072	0.010	0.198	0.843
	Time use	0.360	0.081	0.222	4.422	<0.001

[a]Dependent variable: QoL.

RESULTS

Descriptive Analysis

The study included 362 retirees, as presented in Table I, with a gender distribution equally split between males and females, each comprising 50% of the sample. The median age of the retirees was 66.94 years. Additionally, the majority of the participants were Muslim (61.9%), followed by Hindu (13.5%), Christian (11.0%) and Buddhist (12.7%). The largest ethnic group was Malay (60.8%), followed by Chinese (20.4%), Indian (15.7%) and other indigenous groups (3.1%). Most participants were married (79.8%), and over half had attained tertiary education (52.8%). The majority of participants lived in urban areas (76.0%).

The mean overall EQ score was 74.97, indicating a high health-related QoL among the retirees. The analysis showed that most participants reported no problems with mobility (75.7%), self-care (95.0%), usual activities (81.5%) and anxiety or depression (87.3%). However, a significant number of participants reported some problems with pain or discomfort (42.8%), and a smaller proportion reported extreme problems in self-care (0.6%), usual activities (1.7%), pain or discomfort (1.1%) and anxiety or depression (1.1%).

Regarding time use, retirees reported spending the most time on rest and sleep, with a mean and SD of 10.42 (2.98) hours per day. The mean and SD time spent on instrumental activities of daily living (IADL) was 5.42 (3.40) hours, followed by 3.65 (1.67) hours spent on activities of daily living (ADL). Retirees spent the most time with family, with a mean and SD of 13.91 (7.53) hours, followed by alone time, with a mean of 8.03 (7.28) hours. The least time was spent with friends and spiritual members, with a mean and SD of 0.94 (1.73) and 1.07 (1.80) hours, respectively. Furthermore, retirees reported spending an average of 0.58 hours on productive activities, the least time following retirement.

In terms of role participation, the majority of retirees in this study identified as family members (92.5%, n=335), followed by homemakers (85.4%, n=309) and religious participants (81.2%, n=294). Other roles included care (57.2%, n=207), hobbies (52.2%, n=189), membership in organisations (29.3%, n=106), and volunteering (27.3%, n=99). The mean and SD number of roles reported by the retirees was 5.31 (2.20), indicating that they were engaged in multiple activities. However, only a minority of the retirees reported being students (16.0%, n=58) or workers (16.9%, n=61), suggesting that most retirees were not engaged in formal or informal education or unretirement.

Regarding perceived social support, the retirees reported a relatively high mean score of perceived social support from significant others (20.91±4.48), family (21.17±3.32), and friends (19.99±3.93). The mean and SD for the total score of perceived social support was 62.07 (9.96), indicating that retirees in the study perceived their social support to be moderate to high across all sources.

Table II shows that the multiple regression model examined the relationship between health-related QoL and predictors such as time use, role participation and perceived social support. The R-value of the model was 0.363, indicating a weak but positive correlation between the predictors and the outcome variable. The R Square value of 0.132 suggests that the predictors explain 13.2% of the variance in health-related QoL. The adjusted R Square value of 0.125 is consistent with the number of predictors used in the model. The standard error of the estimate was 12.783, signifying the average distance of the data points from the regression line.

The results of the multiple regression analysis also revealed that role participation and time use were significant predictors of health-related QoL. The model was statistically significant ($F(3, 358) = 18.140$, $p<0.001$), with an R-squared

value of 0.13, indicating that the predictors account for 13% of the variance in health-related QoL. The unstandardised coefficients indicate the effect size of each predictor on the dependent variable, while the standardised coefficients demonstrate the relative importance of each predictor. Specifically, role participation (β = 0.24, p<0.001) and time use (β = 0.22, p<0.001) had a positive influence on health-related QoL. However, perceived social support did not significantly influence health-related QoL (p>0.05).

DISCUSSION

Based on the findings, the retirees in this study had a high level of health-related QoL, indicating that they generally had a positive outlook on life and were satisfied with their current circumstances. This finding is consistent with previous studies showing that retirement can be a fulfilling and rewarding phase of life for many individuals.[24-26]

The high level of health-related QoL observed among the retirees in this study may be attributed to several factors. Firstly, a significant portion of our participants had tertiary education, which positively influenced QoL in older persons, including retirees in Malaysia.[27] This notion is consistent with findings from countries like Iran, where higher education retirees have better retirement adjustment.[28]

Additionally, more than two-thirds of our participants resided in urban areas. While urbanisation might negatively influence QoL in Malaysia,[29] urban retirees often have access to a broader range of resources and opportunities, including cultural events, public transportation and diverse social and recreational activities.[30,31] This access could contribute to their positive outlook and satisfaction with their current circumstances. Furthermore, life satisfaction has been reported to be higher in urban areas in Malaysia,[32] which aligns with our findings of high health-related QoL among urban retirees.

This study aimed to identify the significant predictors of health-related QoL among retirees. The results of this study suggest that time use and role participation are significant predictors of health-related QoL among retirees. These findings are consistent with previous research highlighting the importance of engaging in meaningful activities and maintaining a daily routine for retirees to maintain their QoL.[33,34]

Retirees who engaged in more roles reported higher health-related QoL, which is in line with the theory of role theory, which posits that individuals who occupy multiple roles are likely to have greater self-esteem, a sense of purpose and more opportunities for social interaction, all of which contribute to better QoL.[35,36] These findings suggest that retirees should be encouraged to engage in multiple roles, including family, hobbies, volunteering and organisation membership, to enhance their health-related QoL.

Time spent on rest and sleep was the most significant time use variable for retirees in this study, consistent with the notion that adequate rest and sleep are essential for maintaining physical and mental well-being. However, it is worth noting that the retirees in this study reported spending the least time on productive activities, such as paid work or volunteering. This finding is consistent with previous studies that suggest retirees may experience a loss of purpose and social connection following retirement.[37,38] Therefore, encouraging retirees to engage in productive activities may enhance their sense of purpose and social connection, improving health-related QoL.

Interestingly, the results of this study suggest that perceived social support did not significantly predict health-related QoL. This finding is surprising, as previous research has consistently demonstrated that social support is a crucial determinant of the QoL.[39,40] However, retirees in this study reported relatively high levels of perceived social support, which may have attenuated the relationship between social support and health-related QoL. Future research should further explore the role of social support in predicting health-related QoL among retirees.

These findings have important implications for occupational therapists and other healthcare professionals in identifying appropriate therapies to enhance retirees' health-related QoL. Furthermore, this study contributes to a better understanding of post-retirement time utilisation, role engagement and perceived social support. Health professionals may use this clinically relevant information to promote healthy lifestyles among retirees in Malaysia and beyond.

Future research in this area could explore specific interventions to promote active role participation and time management among retirees, with a focus on improving health-related QoL. This research could also be extended to other populations and contexts, providing valuable insights into how role engagement and time use can impact the health-related QoL of older adults, including retirees.

The study has some limitations. For example, the study may be representative of Malay urban-dwelling retirees in Klang Valley and Malacca with a higher level of education. However, it may not fully represent other retiree groups in Malaysia, especially those from different ethnic backgrounds, rural locations or with lower levels of education. Additionally, the study did not control for potential confounding variables, such as personality traits, influences of fluctuating movement restrictions due to the progression of the COVID-19 pandemic or cultural factors that could have influenced the results. Future studies could include measures of these variables to understand their impact on QoL among retirees better.

Furthermore, the self-report measures used in the study may be subject to response bias or social desirability bias, which could have affected the results. Future studies could aim for a more representative sample to enhance the applicability of the findings. However, despite these limitations, the study provides valuable insights into understanding health-related QoL among retirees, and the findings can inform interventions to promote positive ageing outcomes.

CONCLUSION

In conclusion, this study highlights the significance of effective time management and active engagement in roles to enhance the health-related QoL among retirees, primarily those who reside in urban areas.

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Clinical outcomes of ovarian stimulation with follitropin delta in a mixed regimen with HP-hMG: a real-world retrospective analysis

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ABSTRACT

Introduction: Optimising controlled ovarian stimulation (COS) procedures for in vitro fertilisation (IVF) requires an assessment of the patients' medical history, ovarian reserve, prognostic factors and resources to personalise the treatment plan. Treatment personalisation in IVF is increasingly recognised as being vital in providing a balance of efficacy and safety for patients undergoing the COS procedure. In this study, we aimed to assess the efficacy of an ovarian stimulation protocol employing a personalised dosing algorithm for a novel recombinant FSH (rFSH) derived from a human cell-line - follitropin delta, in a mixed gonadotrophin regimen with human menotrophin (HP-HMG). The main outcome of interest in this study is clinical pregnancy rate (CPR) per embryo transfer cycle.

Materials and Methods: In this single-centre, retrospective, non-interventional study of 20 infertility patients, each individual was provided with a personalised COS regimen based on her ovarian reserve biomarker—serum anti-Mullerian hormone (AMH) and body weight, in a gonadotrophin-receptor hormone (GnRH) antagonist protocol. Personalised dosing of follitropin delta was co-administered with 75 IU of HP-hMG during the COS duration until the final oocyte maturation trigger injection. Ovarian response, pregnancy and safety outcomes resulting from this procedure were assessed and reported here.

Results: Following a mean COS duration of 11 days and 50% of patients who underwent frozen embryo transfers, the CPR per started cycle was 70%. The observed CPR from this study was higher than that reported in the follitropin delta Phase 3 studies using rFSH monotherapy stimulation, and additionally showed no incidents of cycle cancellations and no iatrogenic safety risks such as ovarian hyperstimulation syndrome.

Conclusion: The present study provides a first glimpse into the favourable benefit: risk profile of a mixed protocol regimen using follitropin delta combined with HP-hMG in a cohort of Asian patients in Malaysia.

KEYWORDS:
Assisted reproductive technique, follicle stimulating hormone (FSH), follitropin delta, in vitro fertilisation (IVF), menotropins, ovarian stimulation

INTRODUCTION

The aim of controlled ovarian stimulation (COS) with gonadotrophins for in vitro fertilisation (IVF)/intracytoplasmic sperm injection (IVF/ICSI) is to obtain an adequate number of competent oocytes, leading to improved pregnancy outcomes with minimum risks for the women. However, individual variability in the ovarian and endocrine responses is a well-recognised phenomenon in patients undergoing COS who are given standard doses of recombinant follicle-stimulating hormone (rFSH). This is due to differences in each woman's functional ovarian reserve, genetics and ovarian ageing.[1] It is therefore important to individualise gonadotrophin dosing to tailor the ovarian stimulation according to each patient's profile. The aim of this is to improve the predictability of the ovarian response as well as to eliminate iatrogenic risks, such as ovarian hyperstimulation syndrome (OHSS) or cycle cancellations due to poor response.[2,3]

Follitropin delta (FE 999049, Rekovelle®) is the first recombinant human FSH expressed from a human cell line (PER.C6), resulting in improved stability and higher biopotency compared to other existing rFSH preparations.[4] A unique feature of follitropin delta is its' dosing algorithm which enables treatment personalisation for each individual based on the serum biomarker anti-Mullerian hormone (AMH) and body weight.[4-6] Importantly, this dosing algorithm which was developed specifically for follitropin delta, has been validated in large clinical trials in both the Asian and Caucasian populations.[7,8]

The aim of this non-interventional study is to retrospectively assess the preliminary clinical outcomes resulting from a 'mixed protocol' COS treatment using a combined stimulation with an individualised dosing regimen of follitropin delta and highly purified human menotrophin (HP-hMG) (Menopur®) in the local clinical setting with Asian patients.

The rationale for using a mixed protocol regimen with HP-hMG in COS is due to its evidence of improved clinical outcomes among patients with decreased ovarian reserve or in patients with inadequate response in previous cycles.[9,10] Specifically, HP-hMG (Menopur®) is the only FDA-approved menotrophin with a robust evidence base for application in COS, which provides hCG-driven LH activity during ovarian stimulation and is associated with a higher proportion of mature oocytes and top-quality embryos.[9-15]

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MATERIALS AND METHODS

This was a single-centre, retrospective case series study assessing the efficacy and safety of follitropin delta (Rekovelle®) in combination with HP-hMG (Menopur®) for COS among infertile women aged ≥18 years, who visited the Sunfert International Fertility Centre from July 2021 to February 2023. This study was carried out in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and is approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH). All women were provided written informed consent as part of the retrospective recruitment process. Women were recruited only after the decision to treat with follitropin delta had been made and there was no interference with routine clinical procedures. All data were collected as part of routine clinical practice.

All patients in this study who fulfilled the criteria for ovarian stimulation with a gonadotropin-releasing hormone (GnRH) antagonist protocol were treated with a mixed protocol regimen combining HP-hMG (Menopur®) with a fixed personalised daily subcutaneous dose of follitropin delta.

Two separate syringes were used to co-administer both types of gonadotrophins to all patients - HP-hMG in combination with follitropin delta, with follitropin delta administered at personalised doses determined by an established algorithm based on body weight and serum AMH level.[6] The dose of follitropin delta for each patient may also be conveniently calculated using its online calculator (https://dosedelta.ferring.com/appStart). In contrast to other gonadotrophins, follitropin delta is dosed in µg units instead of International Unit (IU) - which provides a better expression of the biopotency of this new rFSH. As this was a real-world study, physicians were allowed to adjust the doses of gonadotrophins during COS based on clinical discretion. In the case of follitropin delta, any deviation within ± 0.66µg of the calculated dose is considered to be within the range of the drugs' algorithm. The reason for choosing the value of ± 0.66µg is because this corresponds to two minor dial clicks on the Rekovelle® prefilled pen.

All serum AMH measurements were performed within the Sunfert International Fertility centre using the automated Elecsys AMH immunoassay (Roche) as routine baseline clinical evaluation before COS. AMH measurements for all patients are within 12 months prior to the date of starting COS to be considered valid.

Gonadotropin therapy was initiated on day-2 of the menstrual cycle. A gonadotropin-releasing hormone (GnRH) antagonist was initiated on day-6 of stimulation and continued throughout the remainder of stimulation. The response to stimulation was monitored via transvaginal ultrasound (TVUS). HP-hMG (Menopur®) was initiated from day-1 of stimulation at a dose of 75IU, with adjustments of the menotrophin dosing permitted from day-6 of the stimulation cycle. HP-hMG was administered concomitantly with an individualised dose of follitropin delta calculated from the dosing algorithm. In contrast to HP-hMG, no dose adjustments were permitted for follitropin delta throughout the stimulation cycle.

The choice of triggering medication was decided based on serum estradiol (E2) levels; hCG 5,000–10,000 IU was administered if E2 <15,000pmol/L, and GnRH agonist 0.2 mg triptorelin acetate (Decapeptyl®) was given if E2 ≥15,000 pmol/L. A dual trigger of subcutaneous 1,000 IU hCG plus SC 0.2 mg triptorelin acetate may also be administered in patients with low serum LH levels (≤1.0mIU/ml) at the day of trigger. Oocyte retrieval was scheduled 36 hours (±1 hour) after triggering final follicular maturation and injected with ejaculated sperm from a partner. When frozen transfer was indicated, all embryos were cultured to blastocysts, and pre-implantation genetic testing (PGT) for aneuploidy (PGT-A) or monogenic disease (PGT-M) was conducted in cases planned for PGT. All usable blastocysts were cryopreserved for future use. Usable blastocysts are defined as grade 3CC and above according to the modified Gardner grading criteria for blastocyst scoring. Any embryos with a grading of at least one X is not considered usable (Table I). Top-quality blastocysts are defined as those with blastocyst expansion and hatching status 4-6, inner cell mass (ICM) grade A or B, and trophectoderm (TE) grade A or B.

In the frozen cycles, one or two blastocysts could be transferred according to the discretion of the treating physician. The number of thawed blastocysts transfer was determined by age and blastocyst quality, with transfers limited to either one or two blastocysts.

Both natural cycle and programmed regimens were allowed. Daily vaginal progesterone insert (VPI) was prescribed for luteal phase support, with oral dydrogesterone 10 mg tds, according to routine practice of each physician.

The main outcome of interest in this real-world study was clinical pregnancy rate (CPR) at the first transfer cycle. Clinical pregnancy was defined as a pregnancy documented by transvaginal ultrasonography (TVUS) at 6-8 gestational weeks, showing a gestational sac inside the uterus sac with evidence of a fetal heartbeat, excluding all ectopic and biochemical pregnancies. Clinical pregnancy rate was defined as the number of clinical pregnancies divided by the number of embryo transfer cycles. Implantation rate is defined as the number of intrauterine gestational sac(s) (IUGS) observed through TVUS at 3–5 weeks post-transfer divided by the number of embryos transferred.

RESULTS

Baseline Characteristics

A total of 20 patients who attended the Sunfert International Fertility Centre between July 2021 and February 2023 were included in this analysis of our first experience with the novel rFSH follitropin delta used in a mixed protocol stimulation (Table II). Their mean age was 35.2 years; four (20.0%) patients were aged ≥40 years. A majority of subjects were of Chinese ethnicity (80.0%). The study subjects' mean serum AMH level was 26.0±14.71pmol/L, with a mean antral follicle count of 13.0±4.35. Out of this total cohort, two women (10%) were at risk of a hyporesponse to ovarian stimulation on the basis of their low serum AMH level <15pmol/L, while a total of 5 (25%) women were considered high-responders based on their AMH level ≥35pmol/L. The most predominant aetiology for infertility was polycystic ovary syndrome

Table I: The modified Gardner classification scheme (ICM – inner cell mass)

ICM grade	Description	Usability
A	Many cells forming a large compacted ICM	Yes
B	Moderate number of ICM cells, moderate ICM compaction	Yes
C	Few ICM cells, limited ICM compaction or ICM poorly distinguished	Yes
X	No ICM visible or degenerate ICM	No

Table Ib: The modified Gardner classification scheme (TE – trophectoderm)

TE grade	Description	Usability
A	Many cells forming a cohesive TE network (>80 TE cells)	Yes
B	Moderate number of TE cells forming a cohesive network (40-80 cells), some gaps or large TE cells may be apparent	Yes
C	Few TE cells (15-40), large TE cells, irregular network, some unclear TE cell boundaries	Yes
X	Very few TE cells (<15), unclear TE cell boundaries, degenerative or fragmented TE	No

Table II: Demographics and baseline characteristics

Characteristic	
Total number of patients	20
Age (years)	35.2±4.47
Women < 35 years (n, %)	9 (45.0%)
Women 35–40 years (n, %)	12 (60.0%)
Women > 40 years (n, %)	3 (15%)
Race:	
Malay (n, %)	2 (10.0%)
Chinese (n, %)	16 (80.0%)
Indian (n, %)	1 (5.0%)
Others (n, %)	1 (5.0%)
Body weight (kg)	58.3±8.22
BMI (kg/m^2)	23.4±3.67
AMH (pmol/L)	26.0±14.71
AMH (pmol/L)	20.1 (16.0 - 32.7)
AFC - for both ovaries (n)	13.0±4.35
Infertility history	
Duration of infertility (mo)	54.0±32.31
Primary infertility	11/20 (55.0%)
Primary etiology	
Tubal infertility (%)	3/20 (15.0%)
Male infertility (%)	3/20 (15.0%)
Unexplained (%)	3/20 (15.0%)
PCOS (%)	5/20 (25.0%)
Endometriosis (%)	1/20 (5.0%)
Others (%)	4/20 (20.0%)
Smoking (n, %)	1/20 (5.0%)
Number of first IVF/ICSI cycles	16/20 (80.0%)
Number of repeat IVF/ICSI cycles (non-naïve)	4/20 (20.0%)

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.

(Rotterdam criteria) (25.0%); followed by aetiology classified as 'others' (20%). Of the women classified under 'others', one was a potential carrier of a monogenic disorder, one had endometrial cancer, one had unexplained anovulation and another had a bicornuate uterus. Most women (80.0%) were undergoing their first assisted reproductive technology (ART) cycle. None of the subjects had oral contraceptive (OCP) pre-treatment prior to their IVF/ICSI cycle.

Ovarian Response and Safety

All patients were administered follitropin delta in combination with HP-hMG in a mixed protocol stimulation regimen. With regards to follitropin delta, a majority of patients (75%) were dosed according to the specified dosing algorithm, while most of the remaining subjects (20%) were administered an average of 20% higher doses than recommended by the algorithm (range Δ 13.4-23.8µg).

A majority of subjects (95.2%) started with HP-hMG from Day-1 of stimulation, with mean daily dose of HP-hMG administered per subject of 65.2±10.94IU (Table III). The mean duration of ovarian stimulation was 11.0±1.16 days. As this was a mixed stimulation regimen, the mean total dose of follitropin delta co-administered was 96.6±28.2µg, which is approximately equivalent to 1449.0IU of gonadotrophin. Depending on follicular development, some patients were administered a step-down dosing of HP-hMG to mitigate the risk of hyperstimulation (75 IU every alternate

Table III: Ovarian response and pregnancy outcomes

Total patients	20
Duration of stimulation (days)	11.0±1.16
Average daily dose of follitropin delta (mcg)	9.0±2.50
Average total dose of follitropin delta (mcg)	96.6±28.18
Women dosed according to follitropin delta algorithm	15/20 (75%)
Average daily dose of HP-hMG (IU)	65.2±10.94
Average total dose of HP-hMG (IU)	714.3±137.52
Percentage starting HP-hMG from D1 of OS	20/20 (95.2%)
No of cancelled cycles (n, %)	0/20 (0%)
Triggering of final oocytes maturation	
hCG	11/20 (52.4%)
GnRHa	10/20 (47.6%)
No of oocytes retrieved (n)	13.2±6.43
Poor responders (< 4 oocytes) (n, %)	0/20 (0%)
Excessive responders (≥ 20 oocytes) (n, %)	3/20 (15.0%)
Target ovarian response (8–14 oocytes) (n, %)	14/20 (70.0%)
No of MII oocytes (n)	10.8±5.23
Type of fertilization	
IVF	0
ICSI	21
Fertilization rate (%)	67.9±19.93
Blastulation rate (%)	62.6±25.42
Blastocysts:	
Total (n)	5.3±3.52
Top quality (n)	2.4±1.75
≥ 2 cryopreserved blastocysts per cycle start (n, %)	18/20 (90.0%)
No of patients who have undergone embryo transfers (n):	10
Fresh	0
Frozen	10
Average number of embryos per-transfer (n)	1.1±0.32
Implantation rate (%)	72.7%
Clinical pregnancy rate per transferred cycle (n, %)	7/10 (70.0%)
OHSS - any grade (n)	0/20 (0%)

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.

day). If we consider the total dose of gonadotrophin used in this real-world analysis, the sum of the combined administration of both follitropin delta and HP-hMG over an average 11 days of ovarian stimulation is significantly lower than the dosing employed in a conventional protocol ovarian stimulation in our clinic (3164.1±456.08IU vs. 2162.7±469.42 IU; p<0.0001; 95% confidence interval 679.0911, 1323.7089) (Table IV). This comparison of gonadotrophin dose consumption was based on analysis of our historical records of patients with similar baseline characteristics (follow up from Aug 2021-Jan 2023) as a control group reference.

All fertilisation was done by ICSI and resulting embryos were cultured to stage Day 5/6 blastocysts. All blastocysts were vitrified according to standard clinic procedures. At the point of reporting, a total of 10 subjects underwent frozen blastocysts transfer.

For the main outcome of interest in this real-world study, CPR at the first transfer cycle was 70.0% (Table III); most were singleton pregnancies, except for one live birth resulting in twins (from double embryo transfer). Embryos implantation rate (IR) was also similar at 70.0%. In terms of other secondary outcomes, the mean number of total oocytes and metaphase II (MII) oocytes retrieved were 13.2±6.43 and 10.8±5.23, respectively. There were no cycle cancellations (either owing to hyporesponsiveness or risk of hyperstimulation), and no incident ovarian hyperstimulation syndrome (OHSS) among the subjects. Fertilisation and blastulation rates were 62.2%±18.21 and 63.9%±24.11, respectively. Eighteen patients (90%) had at least two or more cryopreserved blastocysts resulting from their first COS cycle.

DISCUSSION

This study represents the first real-world analysis of a combined stimulation protocol with follitropin delta and HP-hMG in a Malaysian population of patients with infertility. In the pivotal Phase III trials - ESTHER-1 and GRAPE, conducted in Caucasian and Asian subjects, respectively, the CPR in these studies were 34.9% and 36.1%.[7,8] The observed CPR per transfer cycle in this study was 70%, which was approximately double the rates reported in the aforementioned trials. There were several salient differences in the protocol and patient populations in both ESTHER-1 and GRAPE compared to our study. In brief, in both of these trials, follitropin delta was administered as a monotherapy COS for a non-inferiority efficacy comparison with conventional rFSH follitropin alfa,[7,8] whereas we employed the mixed protocol stimulation in our study. Pregnancy outcomes were reported following a fresh transfer cycle of either Day 5 (ESTHER-1) or Day 3 (GRAPE) embryos; but in our study, CPR was reported solely from frozen transfer cycles of Day 5/6 blastocysts. Additionally, the mean age of the patients in our study was higher (35.2 years vs. 31.1 years) with a lower median serum AMH (20.1pmol/L vs. 23.4pmol/L) compared to the Asian GRAPE study.[7] This was

Table IV: Comparison of baseline characteristics and ovarian response with historical control group

	Control group	Study group	P valuea	95% CI
Total number of patients	15	20		
Age (years)	33.7±2.46	35.2±4.47	0.2501	-1.1068, 4.1068
Women < 35 years (n, %)	10 (66.7%)	9 (45.0%)		
Women ≥ 35 years (n, %)	5 (33.3%)	12 (60.0%)		
Women ≥ 40 years (n, %)	0 (0%)	3 (15%)		
Body weight (kg)	57.2±7.8	58.3±8.22	0.6915	-6.6903, 4.4903
BMI (kg/m2)	22.1±3.1	23.4±3.67	0.2765	-3.6903, 1.0903
AMH (pmol/L)	27.1±16.7	26.0±14.71	0.8376	-9.7305, 11.9305
AMH (pmol/L) median	21.5 (1.7 - 52.0)	20.1 (16.0 - 32.7)		
AFC - for both ovaries (n)	13.3±5.20	13.0±4.35	0.8538	-2.9865, 3.5865
Duration of infertility (mo)	44.9±26.88	54.0±32.31	0.3829	-30.0352, 11.8352
Duration of stimulation (days)	10.8±0.83	11.0±1.16	0.5746	-0.9178, 0.5178
Average daily dose of gonadotrophin (Control Group: rFSH±hMG or rLH; Study Group: follitropin delta + HP-HMG) (IU)	325.8±43.00	210.6±37.36	<0.0001	87.5072, 142.8928
Average total dose of gonadotrophin (Control Group: rFSH±hMG or rLH; Study Group: follitropin delta + HP-HMG) (IU) (IU)	3164.1±456.08	2162.7±469.42	<0.0001	679.0911, 1323.7089
No of oocytes retrieved (n)	13.3±7.60	13.2±6.43	0.9667	-4.7300, 4.9300
No of MII oocytes (n)	12.1±6.96	10.8±5.23	0.5319	-2.8868, 5.4868
Fertilization rate (%)	66.3±20.26	67.9±19.93	0.8169	-15.5475, 12.3475
Top quality blastocysts (n)	2.3±2.24	2.4±1.75	0.8829	-1.4709, 1.2709

Values are mean±SD, median (interquartile range), or number (percentage), unless stated otherwise.
[a] Two-tailed P value, unpaired t-test.

because the eligibility criteria for patients enrolled in GRAPE was limited to women between 20 and 40 years of age[7], whereas we included subjects ≥40 years old as this was reflective of real-world clinical situation.

Although the mixed protocol stimulation regimen in this study is similar to another trial, registered as the Menopur and Rekovelle Combined Study (MARCS) (NCT03483545), the mean number of top-quality blastocysts in this study was lower at 2.4±1.75, compared with 4.9±3.9 from MARCS.[16] This could be attributed to the higher average daily dose of HP-hMG used in the MARCS trial, which was 133.64±41.12IU vs. 65.2±10.94IU used in this study.[16] Nonetheless, there was a reported OHSS rate of 9.3% among the cohort in MARCS,[16] while there were none in our study, which suggests a lower dose regimen of HP-hMG in our protocol may be a safer approach. The MARCS study did not report on pregnancy outcomes so comparison of this endpoints is not possible.

The gonadotrophin dosing administered from the currently described protocol is 32% lower than our conventional protocol which typically employs between 225 and 300IU/day per COS cycle. Despite this reduced dosage regimen based on the dosing algorithm, there was no compromise on the ovarian response and clinical outcomes as compared to our historical controls with similar baseline characteristics (Table IV). The implication of this finding is that this protocol may be a more efficient and cost-effective methodology for ovarian stimulation.

Overall, despite the more advanced maternal age among our patients (mean age 35.2±4.47) vs. ESTHER-1 (33.4±3.9), GRAPE (31.1±3.7) and MARCS (34.05±3.47),[7-8,16] the resulting stimulation outcomes from this mixed protocol regimen was reassuring and was demonstrated to be safe and efficacious in our local clinical setting with an Asian patient population even at a lower dose of rFSH. Although the use of lower doses of rFSH in IVF/ICSI seems counterintuitive to most clinicians, especially in patients of older age, the present study provides preliminary information that a more personalised dosing regimen based on each patients' ovarian reserve and body weight would not only avoid wastage from overconsumption of gonadotrophins, but it is also markedly safer and provides excellent pregnancy outcomes.

CONCLUSION

Employing a mixed protocol COS regimen with individualised dosing of follitropin delta in combination with HP-hMG results in a good majority of our subjects achieving CPR, without any safety incident of OHSS. By using the validated dosing algorithm for follitropin delta, the total dose of gonadotrophin administered in this protocol was lower than conventional protocol; and thus represents a more resource-efficient, personalised and potentially safer treatment approach for our patients seeking IVF/ICSI treatment.

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Iron burden and endocrine complications in transfusion-dependent thalassemia patients In Sarawak, Malaysia: a retrospective study

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ABSTRACT

Introduction: Thalassaemia is one of the major health problems in Malaysia. With safe blood transfusion regime, the lifespan of patients with transfusion-dependent thalassaemia (TDT) has improved but at the cost of a higher risk of developing endocrine disorders. It is crucial for us to monitor the iron overload to prevent end organ damage. This study aims to evaluate the iron burden and prevalence of endocrinopathies in patients with TDT in Sarawak.

Materials and Methods: This retrospective cohort study was conducted between January 2020 to June 2020 in six government hospitals in Sarawak. A total of 89 patients with TDT, aged 10 years and above, were recruited.

Results: Out of the 89 patients, there were 54 males (60.7%) and 35 females (39.3%) with a median age of 21 years (range 10.0-65.0). Sixty-seven (75.3%) patients had beta-thalassaemia major and 15 (16.9%) patients had haemoglobin E beta-thalassaemia (HbE beta-thalassaemia), remaining seven patients had other genotypes. Thirty-one (34.8%) patients had mean serum ferritin 2500ng/ml and above, and 44 (66.6%) had liver iron concentration (LIC) ≥7mg/g. The prevalence of endocrine disorders in our cohort was 69.7%. The most common endocrinopathies were short stature (n=46, 51.7%), followed by hypogonadism (n=24, 26.9%), delayed puberty (n=23, 25.8%), hypothyroidism (n=10, 11.2%), diabetes mellitus (n=9, 10.1%), impaired glucose tolerance (n=6, 6.7%) and hypoparathyroidism (n=3, 3.3%). Endocrinopathies were significantly associated with age (p=0.01), age at initiating regular blood transfusion (p<0.01) and duration of regular blood transfusion (p<0.01).

Conclusion: Our data shows that the development of endocrinopathies in TDT can be time dependent. Early detection of endocrine-related complications and prompt treatment with iron chelation therapy are important to improve morbidity and mortality. A multidisciplinary approach with good patient-doctor collaboration is the key to improving patient care in our settings.

KEYWORDS:
Transfusion-dependent thalassaemia, iron overload, endocrine complications

INTRODUCTION

Thalassaemia is a common autosomal recessive blood disorder. It is caused by either gene deletion or point mutation that leads to the imbalance of the globin chain synthesis, ineffective erythropoiesis and chronic haemolysis. It has a wide spectrum of clinical manifestations with varying degrees of clinical severity and transfusion requirements. Regular blood transfusions have altered the outlook of the disease by improving patients' survival into the second decade while also preventing growth retardation and skeletal changes. However, with the increasing lifespan, more TDT patients suffer from chronic iron overload with iron accumulation in the liver, heart and endocrine organs.[1]

The Malaysian Thalassaemia Registry (MTR) was formally launched on May 12, 2007, to collect detailed epidemiological and clinical information on patients with thalassaemia in Malaysia. The main purpose of this registry is to enhance care through early detection, optimised treatment, and improved survival. According to the Thalassaemia Registry 2019, 4718 patients are transfusion-dependent.[2] Additionally, it is estimated that 74-140 infants are born with thalassaemia each year.[3] Bone marrow transplantation, a potentially curative treatment for thalassaemia is available in Malaysia but its accessibility is limited due to various reasons such as patient factors and socioeconomic status. Most of the patients still receive regular blood transfusions as part of treatment. Early initiation of iron chelation therapy and close monitoring are crucial to prevent complications of chronic iron overload like heart failure, liver cirrhosis and endocrinopathies.

Sarawak is the largest state in Malaysia housing a large diversity of ethnic groups. According to the Department of Statistics Malaysia, the population of Sarawak in 2019 was

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2.8 million people.[4] There were 265 thalassaemia patients registered in MTR in Sarawak up to November 2019. This gave the prevalence of thalassaemia patients in Sarawak 0.01%. Among those patients that were registered, 44.5% (n=118) were transfusion-dependent, 47.5% (n=126) were patients with non-transfusion-dependent thalassaemia and 8% (n=21) of the patients had succumbed.[2] To date, there is scarce data on patients with TDT with endocrinopathies in Sarawak. Few studies that were conducted have shown a high prevalence of endocrinopathies among this population.[5,6] The risk of developing endocrine complications due to iron overload remains high despite the use of iron chelation therapy. This study aims to assess the iron burden and prevalence of endocrinopathies in patients with TDT in Sarawak.

MATERIALS AND METHODS

Study Design and Study Population

A retrospective, multicentre study was conducted at the haematology clinic or daycare at Sarawak General Hospital, Sibu Hospital, Miri Hospital, Bintulu Hospital, Limbang Hospital and Lawas Hospital. Sarawak General Hospital was the only tertiary hospital with an established haematology service. We retrieved patients with TDT who received treatment and regular follow-ups from these six government hospitals. TDT patients aged 10 years old and above, who received a regular blood transfusion every 2 to 5 weeks to keep the pretransfusion haemoglobin at least 9-9.5g/dL were included. Exclusion criteria were those aged below 10 years old, those with non-transfusion-dependent thalassaemia and those who were cured with bone marrow transplants.

A total of 95 patients with TDT were evaluated. Of these, six patients were excluded from the study as three of them had transferred to other states and we could not retrieve their medical records. A patient with beta-thalassaemia intermedia who required regular blood transfusion had become non-transfusion dependent after undergoing splenectomy. The other two patients with beta-thalassaemia major were less than 10 years old. Thus, a total of 89 patients were recruited for the study.

Data Collection

Data was collected from January 2020 to June 2020. Patients' demographic data, type of thalassaemic syndrome, blood transfusion history, iron burden (mean serum ferritin, liver iron concentration) and iron chelation therapy regime were retrieved from the patient's medical notes. Endocrinopathies were evaluated based on the Tanner staging, growth parameters and blood investigation results based on clinician assessment. The treatment of choice for the iron chelation therapy was based on the iron burden, physician judgement and patient preference.

The patient's full blood count, renal profile, liver function test, serum calcium, serum phosphate and fasting blood glucose were monitored at every clinic visit. Free T4, thyroid-stimulating hormone (TSH), luteinising hormone, follicle-stimulating hormone, oestradiol in females and testosterone in males were measured at least once a year. Iron burden was assessed using serial serum ferritin and liver iron concentration (LIC). Serum ferritin was measured at least twice to thrice a year. Individual ferritin levels were averaged to give a mean ferritin level. MRI T2* imaging was performed once a year to assess the LIC. Serum ferritin ≥2500ng/ml and LIC≥7mg/g were associated with complications related to TDT.[7] We further classified our cohort into serum ferritin<1000ng/ml, 1000-2499ng/ml, 2500-4999ng/ml, 5000-10,000ng/ml and >10,000ng/ml. LIC is classified into LIC<7mg/g, 7-15mg/g and >15 mg/g.

Short stature was defined as height below the 3rd percentile for gender and age based on national growth charts. Delayed puberty was defined as the complete lack of pubertal development in girls by the age of 13 and boys by the age of 14. Hypogonadism was defined in boys as the absence of testicular enlargement (less than 4 ml) and in girls as the absence of breast development by the age of 16. Hypothyroidism was defined as reduced free T4 levels below the lower limit of normal and elevated TSH levels above the upper limit of normal. Diabetes mellitus was defined as fasting glucose >7mmol/L or oral glucose tolerance test (OGTT) serum glucose at 2 hours >11.1mmol/L. Impaired glucose tolerance was defined as OGTT serum glucose at 2 hours >7.8mmol/L and <11.1mmol/L. Hypoparathyroidism was defined as the combination of low serum calcium concentration below the lower limit of normal together with increased serum phosphate above the upper limit of normal and low serum parathyroid hormone level.[8]

Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) software (version 26). The data were assessed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were used to describe the demographic and clinical data. Continuous variables were expressed as median and range. Categorical variables were calculated as frequencies and percentages. Continuous variables between two independent groups were analysed with the independent paired T-test or Mann-Whitney U test. Categorical variables between two independent groups were analysed with the Chi-square test or Fisher's Exact test. The relationship between two quantitative variables was examined using Spearman's rank correlation coefficient. All p values presented were two-tailed, and p values <0.05 were considered statistically significant.

RESULTS

The demographic data, red cell blood transfusion, iron burden and chelation therapy of these 89 patients were summarised in Table I. There were 54 (60.7%) males and 35 (39.3%) females with a median age of 21 years (range 10.0-65.0), comprised of Malay (n=37, 41.6%) and Chinese (n=40, 44.9%) ethnicities, with only a small population from Sarawak indigenous people of Iban (n=1, 1.1%), Kedayan (n=8, 9%), and Bisaya (n=1,1.1%). 2.3% of the patients (n=2) from the area of northern Sarawak were of Kadazan ethnicities from Sabah indigenous people. 67 (75.3%) patients had beta-thalassaemia major and 15 (16.9%) patients had haemoglobin E beta-thalassaemia (HbE beta-thalassaemia). Of the remaining seven patients, one with compound heterozygous Hb Malay/beta+ mutation and beta-thalassaemia Filipino, one with compound heterozygous alpha plus thalassaemia 3.7 deletion with Hb

Table I: Demographic characteristics of patients with transfusion-dependent thalassaemia

Characteristics	Median (range)/no (%)			
	Total (n=89)	Beta-thalassemia Major (n=67)	HbE Beta-thalassemia (n=15)	Others (n=7)
Age (years)	21 (10.0-65.0)	21(10.0-36.0)	25(11.0-49.0)	16 (10.0-65.0)
Age (years)				
10-19	38(42.7)	30(44.8)	4(26.7)	4(57.1)
20-29	31(34.8)	24(35.8)	6(40.0)	1(14.3)
30-39	16(18.0)	13(19.4)	3(20.0)	0(0.0)
40-49	2(2.3)	0(0.0)	2(13.3)	0(0.0)
50-59	1(1.1)	0(0.0)	0(0.0)	1(14.3)
≥60	1(1.1)	0(0.0)	0(0.0)	1(14.3)
Gender				
Male	54(60.7)	41(61.2)	9(60.0)	4(57.1)
Female	35(39.3)	26(38.8)	6(40.0)	3(42.9)
Age of initiating regular blood transfusion (years)	1(0.3-34.0)	1(0.3-7.0)	4(0.5-9.0)	5(1.0-34.0)
Duration of regular blood transfusion (years)	20(2.0-56.0)	20(8.0-36.0)	22(2.0-46.0)	14(4.0-56.0)
Mean annual transfusion volume (ml/kg/year)	198.9(100.0-281.0)	203.5(108.0-281.0)	186.3(100.0-280.0)	181.8(109.0-242.0)
Serum ferritin(ng/ml)				
<1000	14(15.7)	11(16.4)	2(13.3)	1(14.3)
1000-2499	44(49.4)	32(47.8)	8(53.3)	4(57.1)
2500-4999	15(16.9)	10(14.9)	4(26.7)	1(14.3)
5000-10000	13(14.6)	12(17.9)	1(6.7)	0(0.0)
>10000	3(3.4)	2(3.0)	0(0.0)	1(14.3)
LIC(mg/g)[a]				
<7	22(33.3)	19(34.5)	3(33.3)	0(0.0)
7-15	18(27.3)	15(27.3)	1(11.1)	2(100.0)
>15	26(39.4)	21(38.2)	5(55.6)	0(0.0)
Chelation Therapy[b]				
Monotherapy	53(59.6)	39(58.2)	7(46.7)	7(100.0)
Dual therapy	35(39.3)	28(41.8)	7(46.7)	0(0.0)
None	1(1.1)	0(0.0)	1(6.6)	0(0.0)

[a]66 patients had undergone MRI T2* [b]88 patients were on iron chelation therapy

Table II: Association of clinical factors with development of endocrinopathies in TDT patients

Clinical factors	Endocrinopathies		
	Yes	No	p-value
Gender n(%)[a]			0.77
Male	37(59.7)	17(63.0)	
Female	25(40.3)	10(37.0)	
Age n(%)[b]			0.01
years			
10-19	19(30.6)	19(70.4)	
20-29	25(40.3)	6(22.2)	
30-39	14(22.7)	2(7.4)	
40-49	2(3.2)	0(0.0)	
50-59	1(1.6)	0(0.0)	
≥60	1(1.6)	0(0.0)	
Type n(%)[b]			0.62
Beta-thalassaemia Major	48(77.4)	19(70.4)	
HbE β-thalassaemia	9(14.5)	6(22.2)	
Others	5(8.1)	2(7.4)	
Age of initiate regular blood transfusion (mean rank)[c]	38.4	59.8	<0.01
Duration of regular blood transfusion (mean rank)[c]	52.3	28.2	<0.01
Mean annual blood transfusion volume (mean, ml/kg/year)[d]	197.6	202.1	0.65
Serum ferritin n (%)[b]			0.73
ng/ml			
<1000	11(17.7)	3(11.1)	
1000-2499	29(46.9)	15(55.6)	
2500-4999	11(17.7)	4(14.8)	
5000-10000	8(12.9)	5(18.5)	
>10000	3(4.8)	0(0.0)	
LIC n (%)[a] mg/g			
<7	15(31.9)	7(36.8)	0.40
7-15	15(31.9)	3(15.8)	
>15	17(36.2)	9(47.4)	
Chelation therapy n(%)[a]			0.87
Monotherapy	37(59.7)	16(61.5)	
Dual therapy	25(40.3)	10(38.5)	

[a]Chi-square test [b]Fisher's exact test [c]Mann-Whitney U test [d]Independent paired T-test

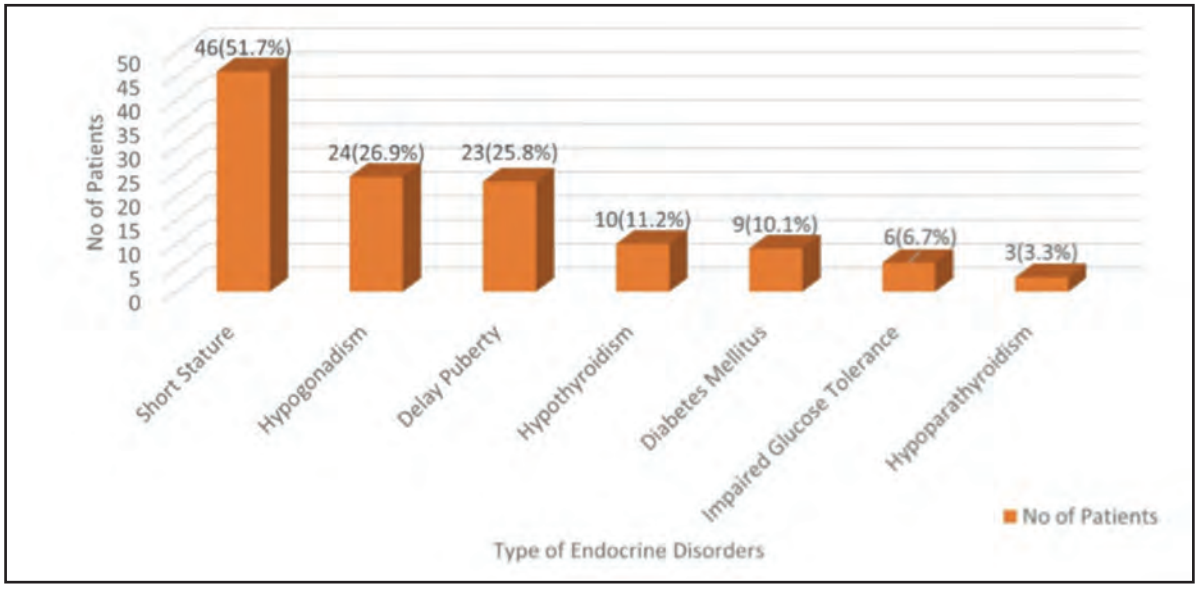

Fig. 1: Prevalence of Endocrinopaties in Transfusion-dependent Thalassaemia

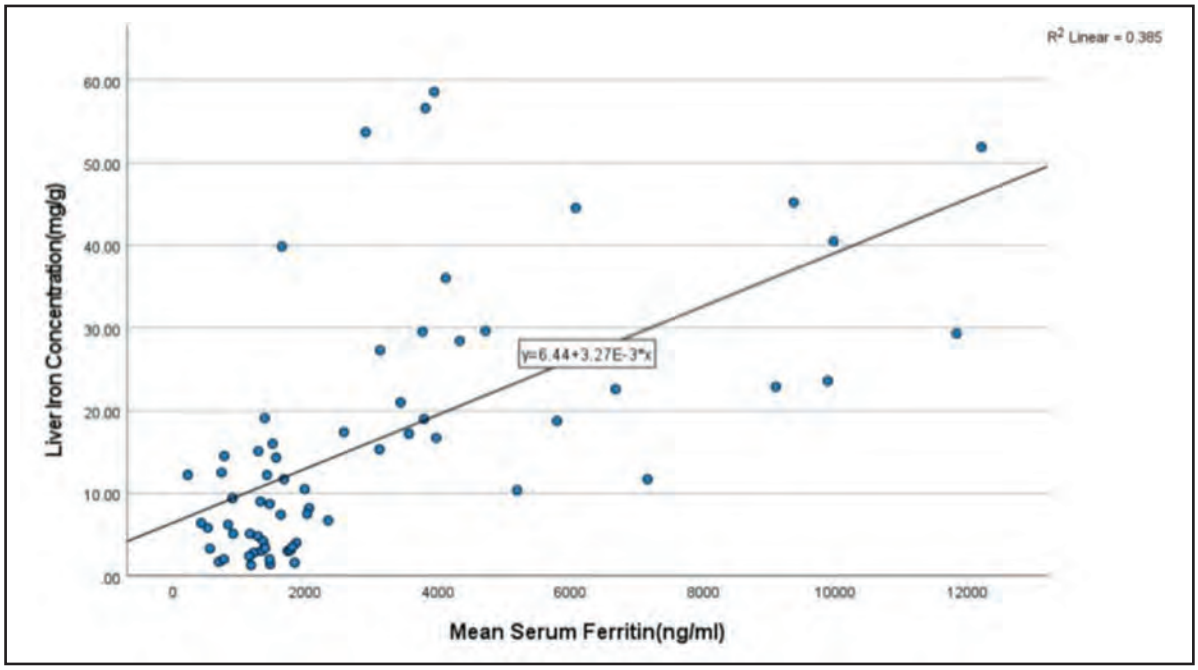

Fig. 2: Simple Scatter of Liver Iron Concentration by Mean Serum Ferritin

Adana, one with concomitant HbH and HbE beta-thalassaemia, one with heterozygous beta-thalassaemia Filipino with Hb Khon Kaen and one with Hb Constant Spring with beta thalassaemia intermedia and two had beta-thalassaemia intermedia with undetermined genotype. In our cohort, patients initiated their first regular blood transfusion at the median age of 1 year old (range 0.3-34.0) with the median years of regular blood transfusion of 20 years (range 2.0-56.0). The mean annual blood transfusion volume was 198.9ml/kg/year (range 100.0-281.0). Iron overload was assessed using the mean serum ferritin and liver iron concentration. In our cohort, 34.8% (n=31) of patients had mean serum ferritin 2500ng/ml and above and 66.6% (n=44) of the patients had LIC ≥7mg/g. 98.9% of the patients (n=88) were on iron chelation therapy, 59.6% of the patients (n=53) were on monotherapy and 39.3% (n=35) were on dual therapy (Table I). Among 53 patients who were on monotherapy, eight patients were on desferrioxamine, 15 patients were on deferiprone, and 30 patients were on deferasirox. For patients who were on dual therapy, 27 patients were on a combination of desferrioxamine and deferiprone while eight patients were on a combination of deferiprone and deferasirox.

The prevalence of endocrine disorders in our cohort was 69.7% (n=62). Among those patients with endocrine disorders, 50.0% (n=31) had one endocrinopathy, 17.7% (n=11) had two endocrinopathies, and 32.2% (n=20) had three and above endocrinopathies. The most common endocrinopathies were short stature (n=46, 51.7%), followed by hypogonadism (n=24, 26.9%), delayed puberty (n=23, 25.8%), hypothyroidism (n=10, 11.2%), diabetes mellitus (n=9, 10.1%), impaired glucose tolerance (n=6, 6.7%) and hypoparathyroidism (n=3, 3.3%) (Figure 1).

Serum ferritin was correlated significantly with liver iron concentration but with poor linearity (R2 = 0.385, p<0.01) (Figure 2). There was no clear association between serum ferritin, liver iron concentration and types of endocrine complications. However, age, age at initiating regular blood transfusion and duration of regular blood transfusion were significantly associated with the development of endocrinopathies (p<0.01) (Table II). Patients with ages 30 years and above have a higher risk of developing at least one type of endocrine disorder (p=0.02). We had done a subgroup analysis of the patient population who was younger than 30 years of age. In this cohort of patients (n = 69), they had a more severe iron burden (n=26, 83.9% had serum ferritin ≥2500ng/ml and n=32, 74.4% had LIC ≥ 7 mg/g) as compared to those who were older than 30 years old (n=5, 16.1% had serum ferritin ≥2500ng/ml and n=11, 25.6% had LIC ≥7mg/g).

DISCUSSION

The availability of safe blood transfusions and iron chelation therapy has resulted in improved disease control and patients' quality of life. For some patients who require regular blood transfusion, splenectomy has prolonged red cell survival and ultimately reduced the red cell transfusion requirement.[9] As we know, the genetic abnormality in thalassaemia syndromes leads to ineffective haematopoiesis. The defective red cells are removed by the spleen which results in splenomegaly. Thus, splenectomy lengthens the life span of red blood cells. This explains why some patients with TDT have become non-transfusion dependent after splenectomy.[9] Generally, the overall survival of patients with TDT has improved significantly and we now face major challenges worldwide with a high global prevalence of endocrine abnormalities.[10,11] In this study population, with a median age of 21 years, more than 2/3 of the patients had at least one endocrine disorder, despite almost all (98.9%) of them receiving iron chelation therapy.

Monitoring iron overload with serum ferritin or liver iron concentration via MRI T2* is crucial to establishing effective iron chelation therapy. Magnetic resonance imaging using the T2* technique to quantify liver iron concentration has become the gold standard because of its safety and reliability. However, the accessibility of MRI T2* imaging in Sarawak remains limited. In our study, there was a significant positive correlation between serum ferritin and liver iron concentrations but with poor linearity (R2=0.385; p<0.01) which is a similar result to other studies.12 This finding shows that serum ferritin can be used as an alternative option for the centres which has difficulty assessing MRI T2* imaging. Serum ferritin remains the method of choice as it is easily available and inexpensive. However, there is a limitation to the use of serum ferritin to monitor treatment response.

The relationship between serum ferritin and body iron stores is not always linear and can change from day to day. Serum ferritin is an acute-phase reactant whose levels can increase with tissue damage and inflammation.[1,13] It is also determined by the types and duration of chelation therapy. Liver iron concentration is more reliable in estimating body iron compared to serum ferritin. As we know, iron tends to accumulate in the liver and eventually in the heart and endocrine systems. LIC should be considered for patients who are on chelation therapy that is monitored with serum ferritin with uncertain responses. The study has shown that the relationship with LIC is not linear when the serum ferritin > 4000 mcg/L and patients may have a fall in LIC without a clear trend in serum ferritin in 6 to 12 months.[1,8] To assess the effectiveness of iron chelation therapy, we need to use LIC to monitor the iron burden. In general, the main goal is to identify iron overload early and optimise chelation therapy to prevent these late effects from happening. Serum ferritin is a convenient way of monitoring treatment outcomes but not without its limits. LIC is reliable but not all of the study population has access to it.

Age, age at initiating regular blood transfusion and duration of regular blood transfusion were significantly associated with the developing endocrine complications in TDT. Our study showed that patients aged 30 years and above had a higher risk of developing at least one type of endocrine disorder, which was comparable to another study in Thailand that occurred above 25 years old.[14] This demonstrates that endocrinopathies in TDT can be time-dependent. Patients with beta-thalassaemia major initiate regular blood transfusion at an earlier age than other genotypes and have a longer duration of regular blood transfusion. As a result, this group of patients is more prone to develop iron overload and endocrine complications. We need to overcome this challenge by early diagnosis of iron overload and initiating iron chelation therapy at a younger age.

Our study showed that endocrinopathy in TDT was related to growth and puberty. 46 patients (51.7%) had short stature, with 27 males (58.7%) and 19 females (41.3%). These findings were comparable to another study.[15] Arab-Zozani et al.,[15] described that male patients had a higher prevalence of short stature compared to female patients. Female patients could tolerate iron overload due to chronic oxidative stress.[15] Studies have demonstrated that Asians with TDT have a higher prevalence of developing short stature compared to Europeans.[5,15,16] The aetiology of short stature in thalassaemia can be multifactorial, which includes chronic anaemia, iron overload, desferrioxamine-induced bone dysplasia, growth hormone deficiency, hypogonadism, hypothyroidism, malnutrition and genetic short stature.[1,8] For patients who have an optimum blood transfusion and developed iron overload, we should investigate for growth hormone deficiency in these groups of patients. However, growth hormone measurement with the insulin tolerance test was not widely available in our settings.

Iron accumulation in the pituitary gonadotrophic cells leads to the development of delayed puberty and hypogonadism in TDT. We found that 26.9% of the patients had hypogonadism, which was comparable to another study in Singapore and Taiwan with similar ethnic populations, 21.9% and 23.1% respectively.[17,18] Our study cohort had a lower prevalence compared to another study done in Italy. The possible cause was that our study population was younger (median age of 21 years compared to 50 years).[10] A systemic review showed that hypogonadism was commonly seen in the older population and more prevalent in patients with TDT, especially those with beta-thalassaemia major.[19] With the advancing age of patients in TDT, we expect to have more patients with gonadal issues. It is therefore important for us to closely monitor them so that we can diagnose them early and initiate prompt treatment with iron chelation therapy and hormone replacement therapy.

This is important for Sarawak and even the whole of Malaysia to implement an effective thalassaemia screening and education programme to ensure thalassaemia is no longer a health burden to the nation. Proper genetic counselling is the key to increasing awareness of the disease, identifying carriers and reducing transmission to the offspring.[20] On the other hand, for paediatric patients with TDT, apart from regular blood transfusion and iron chelation therapy, we should change the direction of treatment. With the presence of HLA-matched related or unrelated donors and even haploidentical donors, haematopoietic stem cell transplantation (HSCT) provides a chance to cure TDT. With the advancement of the HSCT treatment, conditioning regime and control of transplant-related complications have improved over the years.[21] Adult thalassaemia patients have a more advanced disease due to chronic blood transfusion with iron overload and are not candidates for HSCT.

LIMITATIONS

There are a few limitations to this study. The sample size is small and there is a lack of prospective long-term follow-up for endocrinopathies in transfusion-dependent thalassaemia patients. Only 74.2% (n=66) of the patients in this cohort had undergone MRT T2*. Diagnostic tests to investigate endocrinopathies in TDT are not widely accessible. A possible explanation is that these facilities are only available at the tertiary subspecialty medical centre in Kuching which is far from other centres in Sarawak by road or even by air. This is a retrospective study that may not be representative of the general population and is prone to selection bias.

CONCLUSION

In this study, despite the majority of the patients receiving iron chelation therapy, 2/3 of the study cohort had moderate iron overload and a prevalence of endocrinopathies of 69.7%. These findings were higher compared to another study with a similar setting.[6] The findings of this study provide insight into the development of endocrinopathies can be time dependent. However, the limitations of this study require larger studies with more patients to provide more definitive evidence. In conclusion, early detection and close monitoring of complications with individualized therapy are crucial to address these issues, especially at an earlier age to prevent complications in adulthood. Endocrinopathies may increase the overall disease burden when the population ages. Good patient-physician collaboration with a multidisciplinary approach is important to improve the care of patients with transfusion-related endocrine dysfunction.

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DECLARATION OF CONFLICTING INTEREST

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ETHICAL APPROVAL

This study obtained approval from the Malaysian Medical Research and Ethics Committee, Ministry of Health (NMRR-19-3577-51668).

INFORM CONSENT

A waiver of informed consent for this study as it only involved a retrospective review of patients' recorded data.

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ORIGINAL ARTICLE

Prognostic factors for IVF-ICSI live birth rate in women with endometriosis-related infertility

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ABSTRACT

Introduction: The present study aims to identify the factors contributing to diminished successful cumulative live birth rate (LBR) of in-vitro fertilisation-intra-cytoplasmic sperm injection (IVF-ICSI) among patients with endometriosis.

Materials and Methods: In this study, a retrospective cohort investigation was conducted from January 2016 to December 2022 at the Reproductive Medicine Center, Department of Obstetrics and Gynaecology, Sultanah Bahiyah Hospital, Alor Setar, Malaysia. Various determinants influencing substandard cumulative IVF-ICSI LBR prognosis in women diagnosed with endometriosis were analysed. A total of 157 patients, representing 214 IVF-ICSI cycles and 231 embryo transfers, were involved in the current study. The cumulative LBR per cycle was the primary outcome established.

Results: The present study recorded 25.7% (n=55) cumulative LBR per cycle. Prolonged infertility (95% confidence intervals, 95%CI: 0.33, 0.86, p=0.009), moderate to severe endometriosis (95%CI: 0.001, 0.39, p=0.009), and adenomyosis (95%CI: 0.013, 0.98, p=0.048) were factors that significantly reduced the cumulative LBR.

Conclusion: A prolonged infertility duration, the presence of adenomyosis, and moderate to severe endometriosis negatively impacted the cumulative LBR in IVF-ICSI treatments for women with endometriosis. Consequently, early aggressive infertility treatments for patients diagnosed with endometriosis are recommended.

KEYWORDS:
Endometriosis, infertility, IVF, live birth, prognosis.

INTRODUCTION

Endometriosis is characterised by endometrium-like tissue outside the uterus and a chronic inflammatory illness.[1] Primarily, the disease affects females of reproductive age, with an estimated 10 to 15% prevalence.[2,3] Approximately 25 to 50% of infertile women are diagnosed with endometriosis, while 30 to 50% of endometriosis patients experience infertility.[4]

Although historically, endometriosis was believed to affect Caucasians predominantly,[5] recent studies yielded conflicting results regarding racial and ethnic differences in its prevalence.[6-8] Similarly, a report on infertile patients undergoing diagnostic laparoscopy conducted simultaneously in Southeast Asia (Malaysia) and the United Kingdom revealed a considerably higher prevalence of endometriosis among Malaysian women.[8]

Despite being established as affecting fertility, the precise pathophysiology of endometriosis remains unknown. Contemporary perspectives suggest multifactorial mechanisms to explain the effects of the disease, including peritoneal fluid inflammatory alterations which change sperm-oocyte interactions, diminish functional ovarian tissue, and compromise endometrial receptivity.[9]

Typically, assisted reproductive technologies (ART) are employed to manage endometriosis-related infertility. Nevertheless, endometriosis is significantly linked with unsatisfactory in-vitro fertilisation-intra-cytoplasmic sperm injection (IVF-ICSI) results despite its widespread employment in endometriosis patients. Studies also indicated that endometriosis patients exhibited reduced clinical pregnancy rates, ovarian responses, and egg retrieval rates and increased gonadotropin demand than tubal infertility patients.[10-12]

Limited reports are available on identifying prognostic factors in endometriosis patients undergoing IVF-ICSI.[13-15] Furthermore, no studies have assessed the prognostic factors of Southeast Asian endometriosis patients. Consequently, this study aimed to evaluate the prognostic factors influencing the cumulative life birth rate (LBR) in IVF-ICSI among women with endometriosis in the Reproductive Medicine Center, Department of Obstetrics and Gynaecology, Sultanah Bahiyah Hospital, Alor Setar, Malaysia. The present study could be instrumental in counselling local endometriosis patients who seek ART treatment.

MATERIALS AND METHODS

This study obtained ethical approval from the National Medical Research Register (NMRR ID-23-02786-OMI).

The current retrospective study involved 157 subfertile patients from the Reproductive Unit of Department of Obstetrics and Gynaecology, Hospital Sultanah Bahiyah, Alor Star, Kedah, Malaysia. The data were collected from January 2016 to December 2022. The women selected to participate in this study had endometriosis, received IVF-ICSI

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treatment, and were between 18 and 40 years old. Nevertheless, patients with body mass index (BMI) ≥33kg/m^2 or uterine anomalies were excluded.

The personal history and fertility data of each patient were obtained prior to receiving the ART treatment. The information procured included age, race, BMI, infertility type and duration, antral follicle count (AFC) via ultrasonography, presence or absence of other infertility causes (such as tubal or male factors), and the presence of adenomyosis during IVF. This study defined AFC as the total number of antral follicles observed in both ovaries utilising transvaginal ultrasonography during the early follicular phase. Only antral follicles between 2mm and 10mm in mean diameter in the most significant two-dimensional plane across the surface of the ovary were considered for this study.[16]

The current study documented the history and number of endometriosis surgeries before the women received ART treatments, the stage of endometriosis, recurrent endometrioma during IVF, and the interval between surgery and ART. The endometriosis staging was based on the Revised American Fertility Society Classification of Endometriosis guidelines, which were documented during the laparoscopic/laparotomy cystectomy procedure. Whereas, for the ART protocols, this study assessed the IVF attempt rank, controlled ovarian stimulation (COS) protocol, ovarian stimulation period, gonadotropin total dose, retrieved oocyte number, fertilisation rate (number of fertilisations divided by number of mature oocyte), endometrial thickness and numbers of fresh and frozen-thawed embryos transferred.

The COS Protocols

The current study employed the ultralong (gonadotropin releasing hormone [GnRH] agonist administered 3 to 6 months before stimulation), long (GnRH agonist administered during the luteal phase of the previous menstrual cycle) or antagonist (daily administration of GnRH antagonist from day fifth of stimulation) COS procedures. The gonadotropins utilised included recombinant follicle stimulating hormone (r-FSH), follitropin alpha (Gonal F®) and follitropin beta (Puregon®), human menopausal gonadotropin (Menopur®) and r-FSH and recombinant luteinising hormone (r-LH), which combined follitropin alpha and lutropin alpha (Pergoveris®).

The age, total AFC, BMI and previous stimulation dose (if applicable) of the participants in the present study influenced the initial gonadotropin doses administered. In contrast, follow-up doses during the IVF cycle were determined with transvaginal ultrasound. The gonadotropin dosage was adjusted based on the ovarian response during follicular tracking, where the expected follicular growth rate was between 1mm/day and 3mm/day. The GnRH agonist or antagonist and gonadotropin administration were continued until the day of human chorionic gonadotropin (HCG) issuance.

In this study, the patients were given either 10,000 international unit (IU) urinary HCG intramuscularly or recombinant-derived HCG (r-HCG) subcutaneously. The hormone was injected when at least three follicles reached a 17 mm mean diameter. Guided by transvaginal ultrasound, oocyte retrieval was performed 36 hours after HCG administration under local or general anaesthesia. A fresh semen sample from the husband was also obtained on the same day.

Intracytoplasmic sperm injection (ICSI) was performed after denudation and incubating the oocyte-corona complexes for four hours. On the other hand, the luteal phase was supported by daily vaginal progesterone. Progesterone was supplied starting on the oocyte retrieval day until a pregnancy blood assessment was conducted. In this study, fresh embryo transfers typically occurred between 48- and 72-hours post-oocyte retrieval under ultrasound guidance.

In this study, the frozen-thawed embryo transfer (FET) methodology utilised included the modified natural, mild stimulated and artificial cycle approaches. The present study monitored follicular growth in a modified natural cycle via transvaginal ultrasound from the 10th cycle day onwards. Similarly, in the mild stimulated approach, monitoring was initiated from cycle day 10 post daily oral administration of 5mg letrozole during cycle days 2 to 6 to induce mono-follicular growth. The patients subjected to the procedure were regularly monitored every 2 days.

When the dominant follicle recorded a diameter ≥17 mm, HCG was administered to trigger ovulation in the participants. Subsequently, exogenous progesterone was supplied vaginally, starting two days following HCG administration. The embryo transfer period was determined based on the embryo freezing day (5 and 7 days post-HCG administration for 3-day-old embryos and blastocysts, respectively).

In the current study, each participant in the artificial cycle was given 6 mg of oral oestradiol daily with or without prior pituitary suppression with long-acting agonists. Ten days later, an ultrasound evaluation was conducted to measure endometrial thickness and ensure no dominant follicle emerged. Vaginal progesterone suppositories were initiated once the endometrial thickness reached ≥7mm. Embryo transfers were performed three days post-progesterone administration for day-3 embryos, while for blastocysts, 5 days after.

Initially, this study considered pregnancy when a positive plasma HCG level on day 13 after cleavage stage (day-3 embryo) transfer or day 11 after blastocyst transfer. Subsequently, clinical pregnancy was confirmed via ultrasonographic visualisation of one or more gestational sacs, ectopic pregnancy, singleton or twins. Conversely, a miscarriage was defined as pregnancy loss before completing 22 gestational weeks. The present study also recorded delivery of a fertilisation product post completing 22 weeks of gestational age as live birth.

Assessment of Outcomes

Primary objective of our study was determining the cumulative LBR per IVF-ICSI cycle and transfer. This study calculated the cumulative LBR after fresh and frozen embryo transfers for each cycle across the entire population. Furthermore, the characteristics of women who conceived

Table I: The study population and IVF cycle characteristics (total population = 157 and number of cycles = 214).

	n (%)	Mean (Standard Deviation)
Age on the day of ART (years)		32.56 (3.80)
Age group (years)		
< 35	151 (70.6)	
≥ 35	63 (29.4)	
Race		
Malay	192 (89.7)	
Chinese	10 (4.7)	
Indian	7 (3.3)	
Others	5 (2.3)	
BMI		24.36 (4.22)
Infertility duration (years)		6.00 (4.00)*
Infertility types		
Primary	184 (86.0)	
Secondary	30 (14.0)	
Associated tubal factor		
No	136 (63.6)	
Yes	78 (36.4)	
Associated male factor		
No	172 (80.4)	
Yes	42 (19.6)	
History of surgery		
No	12 (5.6)	
Yes	202 (94.4)	
Number of surgeries		
None	12 (5.6)	
One	131 (61.2)	
Two or more	71 (33.2)	
Interval between surgery and ART		
No surgery	12 (5.6)	
< 2 years	130 (60.8)	
≥ 2 years	72 (33.6)	
Associated adenomyosis		
No	129 (60.3)	
Yes	85 (39.7)	
Endometriosis stage**		
I and II	35 (16.4)	
III and IV	149 (69.6)	
Clinical	12 (5.6)	
Unknown (no data)	18 (8.4)	
The rank of IVF attempt		
1st cycle	157 (73.4)	
2nd cycle	50 (23.4)	
3rd cycle	7 (3.2)	
Presence of endometrioma during cycle		
No	139 (65.0)	
Yes	75 (35.0)	
Size of endometrioma during cycle		
< 3 cm	55 (73.3)	
≥ 3cm	20 (26.7)	
COS protocol		
Ultralong agonist	150 (70.1)	
Short antagonist	48 (22.4)	
Long agonist	16 (7.5)	
Antral follicle count (AFC)		8.00 (5.00)*
AFC		
< 5	26 (12.1)	
≥ 5	188 (87.9)	
Gonadotrophin usage		
Only r-FSH	55 (25.7)	
Only hMG	13 (6.1)	
r-FSH + hMG	104 (48.6)	
r-FSH + r-LH	42 (19.6)	
Total gonadotrophin dose		2775.00 (1221.88)*
Duration of controlled ovarian stimulation		10.75 (1.58)
Number of retrieved oocyte		5.00 (4.00)*
Number of mature oocyte		4.00 (3.00)*
Number of fertilisation		3.00 (3.00)*
Fertilisation rate mean		0.86 (0.19)*

Table I: The study population and IVF cycle characteristics (total population = 157 and number of cycles = 214).

	n (%)	Mean (Standard Deviation)
Number of cycle cancelation	1	
Failure to retrieve oocyte	7	
Number of no embryo transfer	10	
Cycles of embryo transfer (ET)		
Number of fresh embryos transferred	153 (66.2)	
Number of frozen-thawed (FET) embryos transferred	78 (33.8)	
FET protocol (n=78)		
Artificial	48 (61.5)	
Stimulated	14 (17.9)	
Natural	16 (20.5)	
Number of embryo transfer		2.02 (0.65)
Day of embryo transfer		3.23 (1.02)
Endometrial thickness (mm)		11.27 (2.36)
Clinical pregnancy per ET cycle		
Fresh	52/153 (34.0)	
FET	21/78 (26.9)	
Miscarriage rate per ET cycle	16/73 (21.9)	
Multiple gestation rate per ET cycle	18/73 (24.7)	
Live birth per ET cycle		
Fresh	41/153 (26.8)	
FET	16/78 (20.5)	
Cumulative clinical pregnancy per cycle	73/214 (34.1)	
Cumulative live birth per cycle	55/214 (25.7)	

(Note: * = median with IQR of non-normally distributed data. ** = endometriosis stage during the surgical procedure based on the Revised American Fertility Society Classification of Endometriosis, ART = assisted reproductive technology; IVF = in vitro fertilisation; r-FSH = recombinant follicle stimulating hormone; hMG = human menopausal gonadotrophin; r-LH = recombinant luteinising hormone.)

and those who did not were compared to establish the prognostic factors influencing ART outcomes. This study also documented cumulative clinical pregnancy rates per cycle and transfer and miscarriage and multiple gestation rates.

Statistical Analysis

All obtained data were analysed with SPSS statistical software. The mean ± standard deviation (SD) in the present study was computed for the continuous variable. On the other hand, categorical parameters were denoted as proportions. The identification of factors associated with cumulative LBR was performed with a binary logistic regression model. Subsequently, all variables linked to a $p<0.25$ in univariate analysis were assessed in a multivariate model. The odds ratios (OR) and 95% confidence intervals (CI) were procured from the coefficients of the model.

RESULTS

The present study was conducted from January 2016 to December 2022 and involved 157 patients. A total of 214 cycles and 231 embryo transfers, including fresh and frozen embryo transfers, were performed during the study. Table I lists the clinical and biological characteristics of the patients and cycles. In this study, the cumulative LBR per cycle was 25.7% (n=55), while the cumulative clinical pregnancy rate per cycle was 34.1% (n=73). Nevertheless, one cycle cancellation (0.47%) due to poor response stimulation was observed, seven cycles (3.27%) documented oocyte retrieval failure and ten cycles with no embryo transfer due to poor embryo quality.

The current study performed multiple logistic regression assessments to identify the prognostic factors of ART outcomes in women with endometriosis receiving treatments in the Hospital Sultanah Bahiyah Reproductive Medicine unit. Simple logistic regression was also conducted to screen for critical independent variable (Table II). Independent variables with a 0.25 p-value were selected as potential candidates for the multiple logistic regression. Nevertheless, all variables were analysed during multiple logistic regression as they were considered clinically crucial. The interpretations of the results are listed in Table III.

Patients with 1-year increase in infertility duration recorded 46.7% lesser chances of having live birth (95%CI: 0.33, 0.86, p=0.009) when adjusted for moderate to severe endometriosis and adenomyosis. The results also revealed that females with endometriosis stages III and IV documented 97.8% less live birth probability than women with mild, clinical and unknown types of endometriosis (95%CI: 0.001, 0.39, p=0.009) when adjusted for duration of infertility and the presence of adenomyosis. Patients with adenomyosis had 88.6% less chances of having live birth than patients without adenomyosis (95%CI: 0.013, 0.98, p=0.048) when adjusted for duration of infertility and moderate to severe endometriosis.

DISCUSSION

The current study recorded a good cumulative LBR (25.7%), a similar rate to most reports.[17-19] Factors that significantly affected LBR after IVF-ICSI in women with endometriosis were also identified, namely prolonged infertility durations, moderate to severe endometriosis and the presence of adenomyosis. The other factors, including age, BMI, types of infertility, surgical history, number and interval of surgeries, associated tubal and male factors, presence and size of

Table II: The prognostic factors of ART outcomes in women with endometriosis receiving treatments in the reproductive medicine unit of Hospital Sultanah Bahiyah assessed through simple logistic regression (number of cycles = 214)

Factors	No live birth, n=159 (n, %)	Live birth, n=55 (n, %)	Regression coefficient (b)	Crude OR (95% CI)	Wald statistic	p-value
Age group						
<35 years (n=151)	108 (50.5)	43 (20.1)	0	1		
≥35 years (n=63)	51 (23.8)	12 (5.6)	-0.53	0.59 (0.29, 1.22)	2.04	0.153
BMI (24.36)	24.50 (4.18)*	23.96 (4.36)*	-0.03	0.97 (0.90, 1.04)	0.69	0.40
Infertility type						
Primary (n=184)	140 (65.4)	44 (20.6)	0	1		
Secondary (n=30)	19 (8.9)	11 (5.1)	0.61	1.84 (0.81, 4.17)	2.15	0.142
Number of surgeries						
None (n=12)	10 (4.7)	2 (0.9)	0	1		
One (n=131)	98 (45.8)	33 (15.4)	0.52	1.68 (0.35, 8.08)	0.42	0.515
Two or more (n=71)	51 (23.8)	20 (9.4)	0.67	1.96 (0.39, 9.75)	0.68	0.411
History of surgery						
No (n=12)	10 (4.7)	2 (0.9)	0	1		
Yes (n=202)	149 (69.6)	53 (24.8)	0.58	1.78 (0.38, 8.38)	0.53	0.467
Interval between surgery and ART						
No surgery (n=12)	10 (4.7)	2 (0.9)	0	1		
< 2 years (n=130)	93 (43.5)	37 (17.3)	0.69	1.99 (0.42, 9.52)	0.74	0.389
≥ 2 years (n=72)	56 (26.2)	16 (7.5)	0.83	1.43 (0.28, 7.20)	0.19	0.665
Adenomyosis						
No (n=129)	90 (42.1)	39 (18.2)	0	1		
Yes (n=85)	69 (32.2)	16 (7.5)	-0.63	0.54 (0.28, 1.04)	3.44	0.064
Endometriosis stage						
I and II (n=35)	24 (11.2)	11 (5.1)	0	1		
III and IV (n=149)	111 (51.9)	38 (17.8)	-0.29	0.75 (0.34, 1.67)	0.51	0.476
Clinical (n=12)	10 (4.7)	2 (0.9)	-0.83	0.44 (0.82, 2.34)	0.94	0.333
Unknown (n=18)	14 (6.5)	4 (1.9)	-0.47	0.62 (0.17, 2.34)	0.49	0.483
Associated tubal factor						
No (n=136)	95 (44.4)	41 (19.2)	0	1		
Yes (n=78)	64 (29.9)	14 (6.5)	-0.68	0.51 (0.26, 1.01)	3.79	0.052
Associated male factor						
No (n=172)	126 (58.9)	46 (21.5)	0	1		
Yes (n=42)	33 (15.4)	9 (4.2)	-0.29	0.75 (0.33, 1.68)	0.50	0.481
Presence of endometrioma during cycle						
No (n=139)	103 (48.1)	36 (16.8)	0	1		
Yes (n=75)	56 (26.2)	19 (8.9)	-0.03	0.97 (0.51, 1.85)	0.01	0.928
Size of endometrioma during cycle						
< 3cm (n=55)	41 (54.7)	14 (18.7)	0	1		
≥ 3cm (n=20)	15 (20.0)	5 (6.7)	-0.02	0.98 (0.30, 3.18)	0.002	0.968
COS protocol						
Ultralong agonist (n=150)	112 (52.3)	38 (17.8)	0	1		
Short agonist (n=48)	38 (17.8)	10 (4.7)	-0.25	0.78 (0.35, 1.71)	0.40	0.527
Long agonist (n=16)	9 (4.2)	7 (3.3)	0.83	2.29 (0.80, 6.58)	2.38	0.123
AFC (8.00)	8.00 (5.00)**	9.47 (4.35)**	0.04	1.04 (0.97, 1.12)	1.11	0.292
AFC						
< 5 (n=26)	21 (9.8)	5 (2.3)	0	1		
≥ 5 (n=188)	138 (64.5)	50 (23.4)	0.42	1.52 (0.55, 4.25)	0.64	0.423
Number of mature oocytes	4.00 (4.00)**	5.00 (5.00)**	0.09	1.10 (1.01, 1.21)	4.86	0.028
Fertilisation rate (0.86, 0.19)	0.84 (0.21)**	0.89 (0.16)**	1.48	4.41 (0.76, 25.49)	2.75	0.097

[Note: N=The total sample size, * = mean with standard deviation as the data is normally distributed and ** = median with IQR as data is not normally distributed. Otherwise, all values are in frequency and percentage.]

Table III: The prognostic ART outcome factors of endometriosis patients treated in the reproductive medicine unit of Hospital Sultanah Bahiyah evaluated with multiple logistic regression (n=214 cycles).

Factors	Regression coefficient (b)	Adjusted OR (95% CI)	Wald statistic	p-valuea
Duration of infertility	-0.63	0.533 (0.33, 0.86)	6.81	0.009
Moderate to severe endometriosis (Stage III & IV)	-3.82	0.022 (0.001, 0.39)	6.73	0.009
Presence of adenomyosis	-2.17	0.114 (0.013, 0.98)	3.92	0.048

[Note: a = likelihood ratio test assessed through the backward stepwise method utilising multiple logistic regression.]

endometriomas, COS protocol, AFC, number of mature oocytes, and fertilisation rate, do not influence the cumulative LBR.

A few studies have reported that a longer duration of infertility led to a considerable adverse effect on IVF outcomes among subfertility causes. Conversely, a systematic review and meta-analysis found a negative association between the infertility period and IVF pregnancy rates (OR: 0.99, 95%CI: 0.98-1.00), suggesting that prolonged infertility duration decreases the chances of pregnancy in IVF.[22]
This study demonstrated that a more prolonged infertility period had a negative impact on the LBR in women with endometriosis. Consequently, women diagnosed with endometriosis should seek fertility treatment earlier. Furthermore, in an IVF meta-analysis investigation of endometriosis patients, Barnhart et al., recommended that females diagnosed with endometriosis of any stage should be referred for aggressive infertility treatment early, including IVF, to increase the chances of conception.[19]

A negative association between LBR in females receiving IVF-ICSI and endometriosis severity was noted in this study. The rate of live birth for stage I and II endometriosis (minimal to mild) was 31.4%, whereas stage III and IV endometriosis, it stood at 25.5%. There is a noteworthy decrease in pregnancy rates with stage III and IV endometriosis (OR 0.022), with the majority of the studied population falling into this category. Two meta-analyses indicated that the IVF outcomes of patients with minimal or mild endometriosis were similar to the results of IVF performed for other indications. Nonetheless, the outcomes were inferior in infertile patients with moderate or severe endometriosis (fewer oocytes retrieved, implantation rate, and birth rate).23,24Harb et al. also reported that the clinical pregnancy rates and implantation in females diagnosed with stages III and IV endometriosis were significantly reduced by 21%.[24]

Although endometriosis and adenomyosis possess comparable histologic features, including endometrial glands and stroma in abnormal locations, the diseases might affect fertility and pregnancy differently.[25] In a cross-sectional investigation, preoperative MRI was performed on endometriosis patients. The report found that 64.7% of histologically proven endometriosis patients had adenomyosis.[26] In this study, the concomitant adenomyosis presence in endometriosis negatively affected the LBR. The results aligned with a few recent meta-analyses that suggested adenomyosis negatively affects reproductive and obstetric consequences.[27-29]

Recently, the debate on the best ovarian stimulation protocol for patients with endometriosis undergoing ART has garnered significant attention. Ultralong GnRH agonist therapy mechanisms have been studied. The approach diminishes the harmful effects of cytotoxic cytokines and oxidative stress on endometriosis patients' ovaries.[30] The ultralong protocol was primarily employed in this study. Moreover, neither GnRH agonists nor GnRH antagonists COS protocols significantly impacted the LBR results.

Cao et al. compared the effectiveness of three GnRH agonist administration protocols (ultra-long, long, and short) in a meta-analysis investigation.[31] The report noted that the ultra-long protocol improved pregnancy rates in randomised controlled trials (RCTs) more effectively than the long protocol. Conversely, the enhancement was not recorded in non-RCTs. On the other hand, protocols with GnRH antagonists documented an immediate pituitary activity interruption post-administration. Despite being similarly effective as GnRH agonists, GnRH antagonists are more advantageous, offering shorter treatment time, ovarian hyperstimulation syndrome risks and gonadotropin dosage and better patient approval.[32]

A meta-analysis conducted in 2023 indicated that long GnRH agonists and antagonists COS protocols generally yielded similar pregnancy outcomes.[33] Goyri et al., also concluded that ovarian stimulation in endometriosis patients did not differ from other stimulated cycles. Consequently, long pituitary suppression treatments with GnRH agonists were replaced with GnRH antagonists due to their shorter treatment and less gonadotropin doses.[32]

The current study noted that the presence and different sizes of endometrioma had no negative impact on the cumulative LBR during an IVF-ICSI cycle. A previous study also reported no significant variation in LBR after IVF-ICSI in patients with endometrioma compared to control patients.[34] Furthermore, the study revealed that endometrioma surgery did not improve the IVF-ICSI outcomes. In another report, poorer IVF result were recorded in patients with decreased ovarian reserve (DOR) post-endometrioma surgery than patients diagnosed with idiopathic DOR.[35] Moreover, the ESHRE guidelines in 2022 recommended that endometrioma surgical procedures should be performed before IVF only in severe pain cases or to improve access to follicles during oocyte retrieval.[1]

Evidence on endometrioma size influences on ART results remain controversial. For instance, some studies suggested that endometrioma size might be relevant and some cysts of particular diameters could result in harmful effects on ovarian responsiveness to stimulation.[36-38] Conversely, a cohort study that included endometrioma of larger sizes indicated that size did not affect the ART outcomes in women with endometriosis-related infertility.[39] The report suggested that a surgical procedure before IVF-ICSI is not necessary. The findings were supported by current information, which indicated that endometrioma cystectomy before IVF did not improve ART results.[1,34]

The present study had some limitations. Firstly, the retrospective and monocentric design diminished the conclusion strength of this study. The sample size was also relatively small, potentially underestimating the significance of specific factors. Moreover, the study population only included women under 40 and BMI <33kg/m2, thus the data obtained could only be extrapolated to patients with similar profiles.

CONCLUSION

The cumulative live birth rate (LBR) in the present study demonstrated a notable decrease linked to extended infertility duration, moderate to severe endometriosis and patients diagnosed with adenomyosis. The findings could hold potential significance in routine clinical practices in advising and guiding couples dealing with endometriosis before opting for ART. Moreover, the results could aid in identifying individuals with diminished IVF-ICSI success prospects, hence preventing unnecessary treatments and allowing exploration of alternative approaches. The present study advocates early and proactive infertility treatment for patients diagnosed with endometriosis. The study is tempered by the small sample size, nevertheless, it could prove valuable for a meta-analytic study.

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ORIGINAL ARTICLE

The outcome of 12-week corticosteroid therapy in COVID-19-related diffuse interstitial lung abnormalities

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ABSTRACT

Introduction: The efficacy of long-course corticosteroid therapy in treating COVID-19-related diffuse interstitial lung abnormalities (DILA) needs to be better understood. We aimed to investigate the benefits of 12-week corticosteroid treatment in COVID-19-related DILA by evaluating computed tomography (CT) lung severity scores.

Materials and Methods: This retrospective, single-centre observational study included patients aged 18 years or older admitted with moderate to severe COVID-19 pneumonia who received 12 weeks of oral prednisolone between January 2021 and December 2021. We recorded clinical parameters, baseline CT scores and post-treatment, modified Medical Research Council (mMRC) dyspnoea scale and pulmonary function tests.

Results: A total of 330 patients were analysed. The mean (standard deviation, SD) age was 54.6 (14.2) years, and 43% were females. Three-point nine per cent (3.9%) require non-invasive ventilation (NIV), while 14.6% require mechanical ventilation (MV). On follow-up at 12 weeks, the CT patterns showed improvement in ground-glass opacities, perilobular density and consolidation. There was an improvement in the mean (SD) CT score before and after prednisolone therapy, with values of 17.3 (5.3) and 8.6 (5.5), respectively (p<0.001). The median mMRC was 1 (IQR 0-1), and 98.8% had a radiological response. The common side effects of prednisolone therapy were weight gain (13.9%), hyperglycaemia (1.8%) and cushingoid habitus (0.6%).

Conclusion: A 12-week treatment with prednisolone showed significant improvement in CT scores with minimal residual dyspnoea and was relatively safe. Longer duration of steroids may be beneficial in moderate to severe COVID-19-related DILA.

KEYWORDS:
Corticosteroid, prednisolone, COVID-19, SARS-CoV-2, diffuse interstitial lung abnormalities

INTRODUCTION

The clinical spectrum of COVID-19 ranges from asymptomatic to severe pneumonia or acute respiratory distress syndrome (ARDS). Prolonged respiratory symptoms or persistent hypoxemia can occur in a subset of patients with COVID-19 pneumonia due to direct viral pathogenicity and hyperimmune response triggering, leading to the destruction of lower respiratory tract airways and alveolar and vascular endothelium. Following COVID-19 infection, persistent parenchymal change is associated with prolonged respiratory symptoms and functional impairment.

Computed tomography (CT) imaging reveals that the abnormalities in these patients often show a combination of ground-glass opacities, perilobular densities and patchy multifocal consolidation consistent with a pattern of organising pneumonia (OP). Histopathologically, this represents diffuse alveolar damage, capillary injury and organising pneumonia. It should be emphasised that most pathological data was from post-mortem specimens and may not reflect survivors' disease course. Transbronchial lung biopsy has been carried out in patients with persistent radiological consolidation in COVID-19 pneumonia and found to have pathological findings of OP.[1]

Steroids have been shown to reduce the inflammation associated with OP, resulting in symptom resolution, improvement in gas exchange and potentially preventing the progression of early parenchymal abnormalities to irreversible fibrosis. However, steroids are associated with adverse effects such as delayed viral clearance, hyperglycaemia and increased susceptibility to infections. Some authors advocate high-dose steroid treatment regimens for a minimum of six months, as proposed for cryptogenic organised pneumonia. However, the question remains whether less intense treatment could resolve the disease in non-idiopathic cases of OP. In COVID-19, studies indicate that the judicious use of corticosteroids in severe COVID-19 may benefit certain patient cohorts but do not recommend routine treatment.[2,3]

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The post-COVID-19 pulmonary sequelae continue to evolve. A prolonged immunologic phase could follow the initial phase of viral replication.[4] Studies mainly concentrate on the role of anti-inflammatory agents during the acute immunologic phase, and little is known about the prolonged use of nonspecific immune modulators such as corticosteroids in patients with COVID-19-related diffuse interstitial lung abnormalities (DILA). Despite the evidence supporting the benefits of corticosteroids in COVID-19, the optimum dose and duration of corticosteroid therapy in different clinical situations and stages of COVID-19 are still being determined due to the substantial heterogeneity of the disease.

During the COVID-19 pandemic, data on the efficacy of corticosteroids have been limited. However, the pandemic has been a powerful stimulus for clinical research addressing the benefits of prolonged corticosteroids for improving lung parenchyma abnormalities and preventing possible fibrosis. To obtain a more comprehensive understanding of the clinical outcomes of COVID-19 treated with long courses of steroids, we conducted a retrospective study analysing CT imaging based on the severity score and the clinical parameters.

MATERIALS AND METHODS

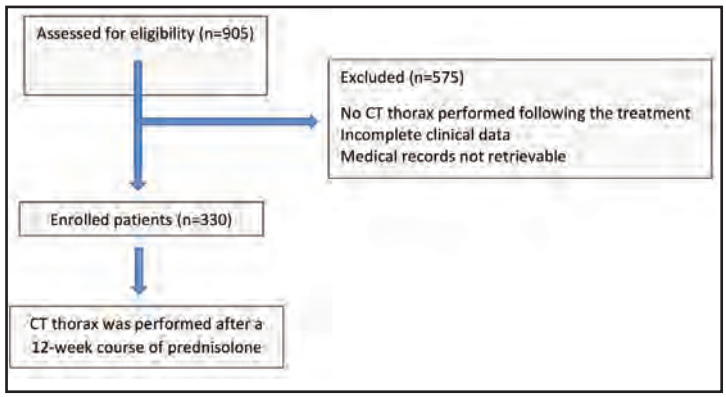
Study Design and Participants

This study was a single-centre, retrospective, cross-sectional analysis of patients with moderate to severe COVID-19 pneumonia treated with a 12-week course of prednisolone at the Teaching Hospital Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz (UKM-HCTM). The study period spanned from January 2021 to December 2021, during the second peak of the COVID-19 pandemic. Inclusion criteria for the study were patients who tested positive for COVID-19 with a positive nasopharyngeal specimen at real-time reverse transcription polymerase chain reaction (RT-PCR) and who received a 12-week course of corticosteroids (prednisone 0.5mg/kg taper over 12 weeks) with available CT thorax before and after corticosteroid treatment. Exclusion criteria included patients who did not undergo CT before and after treatment or incomplete or irretrievable data. This study adhered to the Declaration of Helsinki and was approved by the ethics committee of the UKM-HCTM (HTM-2021-023). The ethics board waived informed consent as the study was retrospective.

Data collection

Data collection involved using a standardised data collection form to retrieve information from the patient's case notes and electronic health record system. Baseline demographic data, clinical history, comorbidities, vital signs, classic COVID-19 symptoms, laboratory values on the day of admission, radiological characteristics, spirometry data, and treatment administered for COVID-19 were manually collected. The chest HRCT images were retrieved and evaluated using picture archiving and communication systems (PACS). Two physicians reviewed the data, and a third physician was consulted to adjudicate any differences in interpretation between the two primary researchers.

Enrolment flow chart of patients with moderate to severe COVID-19:



Lung Imaging Acquisition and CT Quantitative Evaluation

All subjects underwent HRCT (Toshiba Aquilion 640 slices) thorax scan in the supine position during end inspiration. The detailed parameters for CT acquisition were reconstructed at 1.0mm slice thickness, with a 1 mm increment and a sharp reconstruction kernel.

The severity of lung involvement was assessed using a previously described quantitative 25-point CT severity score that is an effective tool in estimating the severity of COVID-19 lung involvement.[5]

CT Severity Score

- A quantitative and a qualitative CT imaging analysis was performed by two blinded expert radiologists with respective 5 years of thoracic imaging experience. Final scores were determined by consensus in case of an inconsistency.
- The CT findings were reported according to the Radiological Society of North America expert consensus document on reporting chest CT findings related to COVID-19.[6]
- Pulmonary abnormalities were quantitatively estimated using a scoring system that assigned a score of 0 to 5 to each of the five lung lobes based on the extent of involvement: 0, no involvement; 1, < 5%; 2, 5-25%; 3, 26-49%; 4, 50-75%; and 5, >75% involvements. Maximum total score was 25.[5]
- The sum of the individual lobar scores constituted the total CT score, which ranged from 0 (no involvement) to 25 (maximum involvement).

The following CT descriptive terms were used: ground glass opacity (GGO), consolidation, interseptal lobar thickening, reverse halo pattern, reticulation or parenchymal band and crazy paving pattern. The chest CT was performed within 2 weeks following the completion of the prednisolone treatment.

Pulmonary Function Tests

In accordance with the American Thoracic Society/European Respiratory Society guidelines, certified technicians conducted outpatient pulmonary function tests within 2 weeks following the completion of the prednisolone treatment.[7] The analysis included forced expiratory volume

Table I: Demographic and baseline clinical characteristics of patients with diffuse interstitial lung abnormalities following COVID-19.

Characteristic	n=330
The severity of the disease, no (%)	
Category 4	285 (86)
Category 5	45 (14)
Gender	
Male: Female	1.3: 1
Age, mean (SD), y	54.6 (14.2)
Age group, No. (%), y	
<18	2 (0.6)
18-29	16 (4.9)
30-39	35 (10.6)
40-49	60 (18.2)
50-59	80 (24.2)
60-69	89 (27)
≥70	48 (14.5)
Duration of symptoms, mean (SD), days.	6.07 (2.75)
Smoking history, No. (%)	
Current-smoker	21 (6.4)
Former-smoker	25 (7.6)
Comorbidities, no (%)	
a. OSA/OHS	6 (1.8)
b. COPD	4 (1.2)
c. Bronchial asthma	10 (3)
d. ILD	0 (0)
Non-respiratory comorbidities	
a. Diabetes mellitus	130 (39.4)
b. Hypertension	183 (55.5)
c. Obesity	22 (6.7)
d. Autoimmune diseases	4 (1.2) RA, MNG, SLE, ITP
e. CKD	14 (4.2)
No comorbidities	73 (22.1)
Pneumothorax/pneumomediastinum, no (%)	9 (2.7)
Initial prescribed treatment, no (%)	
Dexamethasone	65 (19.7)
Methylprednisolone	168 (50.9)
Baricitinib	58 (17.6)
Tocilizumab	50 (15.2)
Tofacitinib	5 (1.5)
Favipiravir	92 (27.9)
Hospital stay, mean (SD), days	16.22 (10.22)

Definition of abbreviations: OSA/OHS = obstructive sleep apnoea/obesity hypoventilation syndrome; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019.

in 1 second (FEV_1), forced vital capacity (FVC), FEV1/FVC ratio, diffusing capacity of the lungs for carbon monoxide (DLCO) adjusted to haemoglobin, DLCO/alveolar volume (VA), and forced expiratory flow 25-75 (FEF25-75). An abnormal value was defined as lower than 80% predicted. Pulmonary function tests (PFTs) with reduced FVC or total lung capacity (TLC) (<80% predicted) but normal or improved FEV1/FVC (>70%) were classified as restrictive ventilatory impairment, while DLCO <80% predicted was considered as diffusion capacity impairment.[8]

Treatment Protocol

Patients diagnosed with DILA are administered systemic corticosteroids when presenting with any of the following indications: i) moderate to severe COVID-19 pneumonia; ii) requiring oxygen supplementation; iii) resting hypoxia with SpO2 <90%. The use of corticosteroids is based on the treatment protocol for inflammatory interstitial lung diseases, such as organising pneumonia and hypersensitivity pneumonitis.[9,10] Although guidelines suggest administering corticosteroids at a dose of 0.5-1mg/kg prednisolone and gradually tapering the dosage over several weeks to months, we have modified the steroid (prednisolone) regime by prescribing 0.5mg/kg body weight over 4 weeks, followed by 20mg daily for 4 weeks, 10mg daily for 2 weeks, and 5mg daily for 2 weeks. Therapeutic interventions were conducted in accordance with the multidisciplinary consensus guidelines on diagnosing and treating COVID-19 established by our centre. In the acute phase of the illness, COVID-19 treatment was initiated upon admission at the discretion of attending physicians, guided by clinical symptoms and CT images.

Outcome of the Treatment

The primary composite outcome was a change in CT scores after a 12-week course of prednisolone therapy. The secondary outcomes assessed were related to prednisolone therapy and included changes in lung physiology and clinical parameters.

Statistical Analysis

In this study, we compared the severity of DILA before and

Table II: Admission symptoms, laboratory values, initial and maximum respiratory support from patients with DILA following COVID-19.

Admission symptoms and laboratory values	n=330
Admission symptoms, no (%)	
Cough	228 (69.1)
Dyspnoea	163 (49.4)
Sore throat	13 (3.9)
Fever	268 (81.2)
Anosmia	21 (6.4)
Diarrhoea	55 (16.7)
Laboratory values on the day of admission, mean (SD)	
Leucocytes, 109/L	8.44 (3.78)
Absolute neutrophil count, 109/L	6.48 (3.57)
Absolute lymphocyte count, 109/L	1.34 (0.68)
Absolute monocytes count, 109/L	0.68 (1.07)
Neutrophils lymphocytes ratio (NLR)	6.06 (4.99)
Platelet count, 109/L	225.83 (94.28)
C-reactive protein, mg/dl	16.4 (77.23)
Ferritin, ug/L	2054.88 (2443.35)
Lactate dehydrogenase, U/L	533.95 (388.87)
D-dimer, µg/ml	3.65 (30.44)
Alanine aminotransferase, U/L	53.33 (42.59)
Alkaline phosphatase, U/L	82.54 (48.34)
Albumin, g/l	32.42 (4.90)
Bilirubin, umol/l	12.68 (8.82)
Blood urea nitrogen, mmol/L	6.14 (6.13)
Creatinine, umol/l	109.76 (123.06)
PaO2/FiO2, mmHg on presentation, mean (SD)	236.6 (107.08)
RS on presentation, no (%)	
Nasal prong	145 (43.94)
Rebreather mask (FM+VM)	81 (24.55)
High-flow non-rebreather mask	44 (13.33)
HFNC	11 (3.33)
CPAP	5 (1.52)
BiPAP	3 (0.91)
MV	8 (2.42)
Maximum RS, no (%)	
Nasal prong	82 (24.85)
Rebreather mask (FM+VM)	66 (20)
High-flow non-rebreather mask	78 (23.64)
HFNC	38 (11.52)
CPAP	5 (1.52)
BiPAP	8 (2.42)
MV	48 (14.55)

Definition of abbreviations: PaO2/FiO2: arterial oxygen tension/inspiratory oxygen fraction; RS: respiratory support; FM: Face mask; VM: Venturi mask; HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure; BiPAP: Bilevel positive airway pressure; MV: mechanical ventilation.

Table III: Results after structured assessment of patients with DILA treated with a 12-week course of prednisolone after COVID-19.

Parameter	n=250
mMRC upon clinic follow-up (IQR)	1 (0-1)
6 MWT distance, m	274.34 (75.92)
6 MWT desaturation (SpO_2 dropped > 3%), no %	47 (18.88)
Full lung function test	
FEV_1, L	2.18 (0.62)
FEV_1, % of predicted	84.34 (16.76)
FVC, L	2.62 (0.74)
FVC, % of predicted	74.91 (14.68)
FEV_1/FVC, % median	82.48 (7.73)
FEF 25-75, L	2.77 (1.16)
FEF 25-75% predicted	97.05 (37.59)
DLCO adj, L	17.83 (7.41)
DLCO adj, % of predicted	81.77 (36.2)
DLCO/VA, L	4.36 (0.99)
DLCO/VA, % of predicted	108.31 (22.64)

Definition of abbreviations: 6MWT = 6-minute walk test; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; MRC = Medical Research Council; SpO_2 = oxygen saturation as measured by pulse oximetry; TLCO = transfer factor of the lung for carbon monoxide. Data are presented as mean + standard deviation unless otherwise stated.

Table IV: CT pattern at baseline and after a 12-week course of prednisolone.

CT pattern	Baseline n (%)	After a long course of prednisolone n (%)
GGO	323 (97.88)	314 (95.15)
Perilobular density	269 (81.52)	107 (32.42)
Consolidation	239 (72.42)	11 (3.33)
Crazy paving	42 (12.73)	4 (1.21)
Septal thickening	10 (3.03)	2 (0.67)
Parenchymal band/reticulation	28 (8.48)	184 (55.76)
Reverse halo sign	14 (4.24)	0

Table V: Baseline CT score versus CT score after a 12-week course of prednisolone therapy.

Lobe involved	Baseline CT score	CT score after prednisolone therapy	p-value)
RUL	3.30 (1.28)	1.54 (1.18)	p<0.001
RML	2.94 (1.43)	1.41 (1.12)	p<0.001
RLL	3.91 (1.09)	1.83 (1.25)	p<0.001
LUL	3.26 (1.27)	1.57 (1.20)	p<0.001
LLL	3.92 (1.10)	1.82 (1.31)	p<0.001

Definition of abbreviations: RUL = right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe. Data are presented as mean (SD).

Table VI: Analysis of the confounding factors.

CT score	Ventilated	Not ventilated	p-value
Baseline CT score	18.5 (5.3)	17.3 (5.3)	0.646
CT score after treatment	10 (6.2)	8.6 (5.5)	0.724
	With tocilizumab	Without tocilizumab	
Baseline CT score	20.1 (5.2)	16.8 (5.1)	<0.001
CT score after treatment	9.5 (6)	8.5 (5.4)	0.225
	With baricitinib	Without baricitinib	
Baseline CT score	17.1 (4.9)	17.3 (5.4)	0.786
CT score after treatment	9 (5.5)	8.5 (5.5)	0.589

Notes: The result is presented as mean (standard deviation).

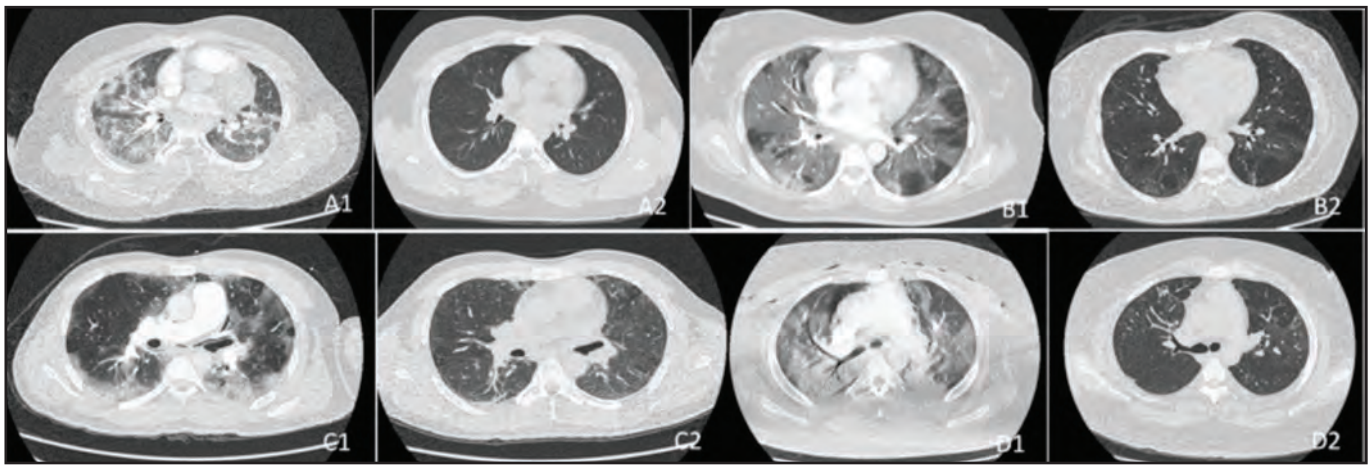


Fig. 1: Axial chest HRCTs suggest a significant improvement in CT scores after CS therapy. (A1) Pre-CS: consolidation and perilobular density of RML, RLL, and LLL. (A2) Post-CS: minimal linear parenchymal bands. Reduction of CT score, consolidations and perilobular density. (B1) Pre-CS: extensive GGO and the arcade-like all lobes. (B2) Post-CS: residual GGO and linear parenchymal bands. Reduction of CT score and GGO. (C1) Pre-CS: peripheral consolidation and GGO of all lobes. (C2) Post-CS: GGO and reticulation. Reduction of CT score, consolidations and GGO. (D1) Pre-CS: extensive consolidation of all the lobes, pneumomediastinum and subcutaneous emphysema. (D2) Post-CS: complete regression of consolidations and pneumomediastinum with residual reticulation. Reduction of CT score and resolution of consolidation and pneumomediastinum.

Definition of the abbreviation: CS, corticosteroid; GGO, ground glass opacity; HRCT, high-resolution computed tomography; LLL, left lower lobes; RML, right middle lobe; RLL, right lower lobe.

after a 12-week course of prednisolone therapy by analysing the CT scores and exploring the association between these variables. Categorical data were presented as numbers and percentages, while continuous variables were expressed as median and interquartile range (IQR) or mean and standard deviation. The Student's t-test was used for normally distributed continuous variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. The changes in CT scores were assessed using an independent samples T-test. Adverse events and radiology findings were reported descriptively. Categorical variables were compared using a chi-squared test or Fisher's exact test, as appropriate. Pearson's correlation coefficient and Cox regression examined the relationship between variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26; SPSS, Chicago, IL, USA).

RESULTS

Demographic Data

The present study assessed a cohort of 905 patients, of which 575 were excluded based on predetermined criteria that included no CT thorax performed following prednisolone treatment, incomplete clinical data, or medical records not retrievable. The mean (SD) age of the enrolled patients was 54.6 (14.2) years, with a range spanning from 14 to 84 years. Females constituted 43% of the cohort. The prevalence of current smokers was 6.4%, whereas non-smokers and former smokers accounted for 86% and 7.6% of the cohort, respectively. Tables I and II outline patients' demographic and baseline clinical characteristics with DILA following COVID-19.

Clinical Characteristic

On presentation, 268 (81.2%) patients manifested fever, while nearly half presented with cough and dyspnoea (69.1% and 49.4%, respectively). The mean (SD) duration from symptom onset to deterioration was 6.95 (4.61) days. Of the cohort, 257 (77.9%) had pre-existing medical conditions, with hypertension being the most common comorbidity (n=183, 55.5%). Among respiratory comorbidities, bronchial asthma was the most prevalent, observed in 10 (1%) patients. Fifty-eight (17.6%) patients were diagnosed with pulmonary embolism during the acute phase of COVID-19.

Upon presentation to the emergency department, 297 (90%) required oxygen supplementation, and 48 (14.6%) required mechanical ventilation, with a mean (SD) duration of ventilation of 8.73 (6.65) days. Throughout hospitalisation, methylprednisolone was the most frequently administered therapy (50.9%). The mean (SD) hospital stay was 16.22 (10.22) days, with 11 patients (3.3%) staying for five days or less, 101 (30.6%) for 6-11 days, 97 (29.4%) for 11-15 days, and 121 (36.7%) for more than 16 days. Twelve (3.64%) patients required home oxygen upon discharge.

The side effects of long-course steroids include weight gain, uncontrolled diabetes mellitus, infection (one pulmonary tuberculosis, one MSSA bacteraemia, one herpes infection) and others (two cushingoid, three hair loss, two acnes, one insomnia, two dyspepsia)

Laboratory Parameter

At the time of presentation, 16 (4.8%) patients had leucopenia, 98 (29.7%) had lymphopenia, eight (2.4%) had neutropenia and 59 (17.9%) had thrombocytopenia. Of the total cohort, 322 (97.6%) patients had lactate dehydrogenase levels > 220 U/L, 313 (94.8%) had CRP levels >1mg/dL, and 31 (9.4%) had D-dimer levels >4µg/mL. The mean (SD) ferritin level was elevated at 2054.88 (2443.35) µg/L. Liver enzymes were elevated (>2 times the upper normal limit) in 53 (16.06%) patients. There was no significant correlation between the baseline CT score and the NLR, CRP, and ferritin levels upon the initial presentation to the hospital.

Pulmonary Function Test

A total of 250 (75.8%) patients underwent full lung function testing after receiving a 12-week prednisolone treatment (Table III). The mean post-treatment values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DLCO) was 2.18 L (84.4% predicted), 2.62L (74.9% predicted), and 17.83L (81.8% predicted), respectively. Of the patients, 163 (65.2%) had FVC impairment (FVC <80% predicted). Impairment of FEV1/FVC (FEV1/FVC <0.7) was observed in 13 (5.2%) patients. Mild DLCO impairment was present in 71 (28.4%) patients, moderate impairment in 46 (18.4%), and severe reduction in DLCO in 3 (1.2%) patients. After treatment, there were significant negative correlations ($p<0.05$) observed between CT scores and DLCO ($p=0.003$), FVC ($p=0.004$), as well as FEV1 ($p=0.042$), with higher CT scores being associated with lower values of DLCO, FEV1, and FVC.

Radiological Features

We found a complete radiological response in four (1.2%) subjects. The three most common baseline CT patterns were GGO (323, 97.9%), perilobular density (269, 81.5%) and consolidation (239, 72.4%). Following a 12-week course of prednisolone treatment, the most common CT patterns observed were GGO in 314 patients (95.2%), parenchymal band/reticulation in 184 patients (55.8%) and perilobular densities in 107 patients (32.4%). The patterns of lung changes are depicted in Table IV.

CT Severity Score

In terms of oxygenation and length of stay (LOS), patients with a higher baseline CT score (CT score >10) had significantly worse parameters than those with a lower CT score (CT score ≤10): the median (IQR) PaO2/FiO2 ratio on presentation was lower [230 (145-300) vs. 300 (236-365), $p<0.001$], and the median duration of hospitalisation was longer [14 (10-21) vs. 10 (7-12) days, $p<0.001$].

The mean (SD) CT scores at baseline and after treatment for each lung lobe were depicted in Table V. The mean (SD) baseline total CT score was 17.3 (5.27), and after treatment, it was 8.61 (5.48). There was a significant improvement in the mean (SD) CT severity score after a 12-week course of prednisolone treatment compared to the baseline score [8.6 (5.5) vs. 17.3 (5.3), $p<0.001$]. Figure 1 depicts the change in CT findings before and after treatment in patients with post-COVID-19 DILA.

DISCUSSION

While most COVID-19 patients manifest mild symptoms, a significant portion may experience prolonged inflammation that results in persistent respiratory symptoms and imaging abnormalities, as documented in prior studies.[11-12] The COVID-19 virus can trigger the secretion of cytokines, which can lead to severe alveolar injury. The question of whether prolonged corticosteroid therapy should be utilised to treat diffuse parenchymal abnormalities in COVID-19 patients remains a highly debated topic. Lung autopsy findings have shown diffuse alveolar injury with cellular fibromyxoid exudate, interstitial mononuclear inflammatory infiltration and hyaline membrane formation, resembling acute respiratory distress syndrome (ARDS).[13] These findings suggest that increased immune and inflammatory responses mediate the COVID-19 virus infection and that the severity of the disease is correlated with immune factor concentrations. This study describes the clinical and radiological outcomes observed in a large cohort of patients with moderate to severe COVID-19 DILA following their initial hospitalisation. The patients were administered 12-week course of oral prednisolone to avert the onset of pulmonary fibrosis and permanent functional deficits.

Corticosteroids are a class of immunosuppressive drugs that exhibit anti-inflammatory properties, reducing systemic inflammation. In COVID-19 pneumonia, corticosteroids can have beneficial and deleterious effects depending on the stage of infection. Early administration of corticosteroids may suppress host antiviral activity and promote viral replication and alveolar epithelial cell cytopathic damage. However, in the later stages of infection, corticosteroid therapy can reduce proinflammatory cytokines, enhance anti-inflammatory cytokines and pro-resolving lipids, improve epithelial barrier integrity, decrease lung vascular permeability, and promote alveolar oedema fluid clearance. Studies reported administration of corticosteroids in the hyperinflammation stage in COVID-19 patients may suppress the cytokine storm and improve oxygenation, but the results were inconsistent.[14-16]

It has been reported that CT evidence of air trapping corresponds to postviral constrictive bronchitis, while GGO corresponds to post-OP and post-DAD fibrosis.17 Cryptogenic OP has been studied to understand the clinical and imaging patterns of OP in COVID-19.[18] OP is typically highly responsive to steroids, with opacities that improve or resolve with treatment, although residual fibrosis may occur. This residual fibrosis often has a pattern that resembles nonspecific interstitial pneumonia with basilar predominant reticulation, traction bronchiectasis, and subpleural sparing.[19]

Several randomised trials suggest that systemic corticosteroids enhance clinical outcomes and reduce mortality among hospitalised COVID-19 patients requiring supplemental oxygen.[20,24] However, managing COVID-19-related DILA remains unclear. Some physicians take a 'wait-and-see' approach, while others administer prolonged corticosteroids to patients with persistent symptoms and DILA.[22] Duration of corticosteroid use ranges from 3 to 11 weeks, and studies have shown that this treatment improves clinical symptoms, oxygenation, and radiological abnormalities. Glucocorticoids have been reported to improve diffuse parenchymal lung abnormalities in symptomatic COVID-19 patients, though the complete radiological response is rare.[22] Approximately 22% of severe COVID-19 patients show radiological improvement at 12 weeks, with 38% showing improvement at six months.[23] A meta-analysis suggests that corticosteroids are associated with lower mortality among critically ill patients, whether or not they receive invasive mechanical ventilation.[24] The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial found that 6mg/d of dexamethasone led to a 2.8% absolute reduction in mortality, with the most significant benefit observed in patients receiving invasive mechanical ventilation or oxygen alone. However, potential harm was noted in patients not requiring oxygen.[25] A study indicated that administering oral methylprednisolone at 0.5mg/kg/day for 4 weeks improved radiological abnormalities, oxygen saturation, FVC and 6-minute walking distance in post-COVID-19 ILD.[26] The question remains whether post-COVID-19-related DILA will resolve spontaneously or due to the effects of corticosteroid therapy. Some patients may require more extended corticosteroid therapy to achieve symptomatic relief and radiological improvement. In this study, patients with COVID-19-related DILA and hypoxic respiratory failure were given a trial of corticosteroids in tapering doses over 12 weeks.

Chest CT plays an important role in both diagnosing COVID-19 pneumonia and assessing the extent of lung involvement. Several studies have demonstrated a strong correlation between the 25-point CT score and the clinical severity and outcome of COVID-19 infection.[5] Additionally, these studies have found a positive association between CT scores, inflammatory markers, and oxygen requirement, which helps define the severity of the disease.[5] Quantitative CT analysis has proven to be a valuable tool for monitoring the severity of COVID-19 pneumonia and evaluating treatment response, with consistently high reproducibility in results.[26] Study also demonstrated strong interrater reliability between radiologists regarding the CT score.[27] Our study assesses corticosteroid treatment response in COVID-19 using quantitative CT analysis. Our findings indicated that prednisolone therapy had a beneficial effect in expediting the recovery of compromised lung function in patients with moderate to severe COVID-19 pneumonia, as evidenced by the CT score.

The reported CT sequelae commonly observed after COVID-19 infection include pulmonary interstitial changes, which include ground-glass opacities (GGO) and irregular lines that may persist for beyond six months.28 Additionally, more severe cases of COVID-19 have been linked to increased fibrosis, bronchial dilatation, parenchymal bands, and coarse subpleural reticulation. A study indicated that patients who survived ARDS caused by COVID-19 were more likely to exhibit fibrotic changes. These survivors tended to be older, male, with lower BMI, longer duration of oxygenation requirement (MV or HFNC duration), and worse sedative status.[29,31] Another study revealed that persistent interstitial lung abnormalities were still evident in 2-year follow-up CT scans, with approximately one-fifth showing fibrotic

abnormalities.28 In the present study, the most common CT findings were the peripheral distribution, GGO, consolidation, and crazy-paving pattern. However, whether all these radiographic lesions eventually resolve, become permanent, or progress over time remains uncertain based on this data and the available medical literature.

In COVID-19, pulmonary function tends to improve over time, although it may persistently remain impaired in some patients for several months or even years.[32,33] The reduction of respiratory function observed after COVID-19 were more pronounced in patients who developed ARDS. In our group of patients, approximately half exhibited a decline in DLCO during follow-up, and those with higher CT scores showed greater DLCO impairment. These findings align with previously reported studies. Autopsy findings from COVID-19 cases have shown varying degrees of alveolar destruction and interstitial fibrosis, which may partially account for the impaired DLCO. Interestingly, a small percentage of patients with no residual imaging abnormalities displayed a decrease in DLCO. We hypothesise that this group of patients might have residual microcapillary or alveolar abnormalities post-COVID-19 infection. The residual dyspnoea in our patient cohort underscores the need for specific attention to address this issue. Patients experiencing persistent dyspnoea and impaired DLCO or DILA should be offered pulmonary rehabilitation to improve their lung function.

It is worth mentioning that although only a small percentage of the study cohort received tocilizumab (15.25%) and baricitinib (17.6%), there was an observed improvement in the CT score post-treatment (Table VI). However, this result should be approached with caution since even those who didn't receive tocilizumab or baricitinib also exhibited some improvement in CT scores after treatment, likely attributable to prednisolone treatment. This observation aligns with another study where no significant differences were noted in CT scores 14 days post-treatment with tocilizumab.[34] The authors of that study suggested that the semi-quantitative assessment of lung involvement, relying on visual scoring of lobar extent, might have limitations in detecting subtle density changes, especially in short follow-up assessments.[34] While baricitinib has demonstrated effectiveness in reducing the need for invasive mechanical ventilation and mortality in COVID-19 patients, there hasn't been any study specifically examining its impact on CT scores.[35] Another factor analysed for potential confounding effects was the CT scores between ventilated and non-ventilated patients. Although the baseline CT score was higher in the ventilated group, the difference did not reach statistical significance (Table VI). However, it's noteworthy that the baseline CT score proved to be informative, as a previous study demonstrated that semiquantitative chest CT analysis at hospital admission accurately identified patients who were less likely to respond well to non-invasive positive pressure ventilation.[36]

In the absence of a control arm in our study, we conducted a comprehensive literature review focusing on the natural course of post-COVID-19 CT changes and studies utilising a similar CT severity scoring system to evaluate the progression of CT findings. A study involving patients treated with a combination of methylprednisolone and tocilizumab revealed mean (range) CT scores for categories 4 and 5 COVID-19 during hospitalisation and 3-month follow-up to be 14.7 (6.5-24) versus 8.3 (2.5-20) and 16.9 (11-22.5) versus 10.4 (3.5-18.5), respectively.37 Another study administering steroids during the acute phase of COVID-19 demonstrated mean (SD) CT scores based on ground-glass opacities (GGO) and consolidation patterns at baseline and 18 months as 20.9 (11.2) vs. 11.1 (5.6) and 7.7 (6.8) vs. 1 (1.7), respectively.[38] Studies focusing on COVID-19 patients with bilateral pulmonary involvement treated with a combination of steroids and intravenous immunoglobulins indicated CT scores at baseline and 8-week follow-up of 10.8 (4.3) vs. 14.5 (6.5), respectively.[39] Meta-analysis indicated that about 32% of the patients had residual CT abnormalities of ground glass opacity and fibrotic-like 1 year after COVID-19.[40] Compared to these studies, our patient cohort exhibited notable improvement in CT scores following 12 weeks of prednisolone treatment.

LIMITATION

This study has several limitations, including its retrospective design and the fact that it was conducted at a single centre, which may introduce selection biases. Additionally, the study only included a subgroup of patients who received 12 weeks of corticosteroid and underwent post-treatment CT scans, potentially limiting the generalizability of the findings to the larger population of COVID-19 patients with diffuse interstitial lung abnormalities.

CONCLUSION

We observed that a 12-week course of systemic corticosteroids resulted in radiological improvement in moderate to severe COVID-19-related diffuse interstitial lung abnormalities (DILA) cases. We found the safety profile of corticosteroid usage to be acceptable. However, corticosteroid therapy should be individualised and tapered off as soon as clinical stability and radiological improvement are achieved. It is unclear if COVID-19-related organising pneumonia or DILA is linked to the risk of progressive pulmonary fibrosis or if corticosteroid treatment might lower the risk. Still, these ideas should be carefully looked at in future studies.

Figure 1. Change in CT findings before and after treatment with a 12-week course of prednisolone in patients with post-COVID-19 diffuse interstitial lung abnormalities.

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ORIGINAL ARTICLE

A retrospective review of antiphospholipid syndrome: a single tertiary centre experience

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ABSTRACT

Introduction: Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). Our study aims to study the clinical and laboratory characteristics, treatment strategies and outcomes of APS patients retrospectively.

Materials and Methods: A retrospective review of all APS patients treated in Rheumatology Unit, Hospital Pulau Pinang between October 2021 and October 2022 was conducted.

Results: A total of 53 APS patients (age 42.4±13.9 years) including 22 (41.5%) primary and 31 (58.5%) secondary APS patients were identified. Thrombosis was the most common clinical manifestation (51/53; 96.2%) followed by pregnancy morbidity (15/45; 33.3%). For other clinical manifestations, aPL-associated thrombocytopenia was the most frequently observed manifestation (26.4%) followed by autoimmune haemolytic anaemia (18.9%). Lupus anticoagulant (LA) (88.7%) was the most commonly found aPL followed by anticardiolipin antibody (aCL) (50.9%) and anti-beta 2 glycoprotein 1 antibody (B2GP1) (30.2%). 10 (18.9%) patients tested positive for all three aPL. The majority of our patients (86.8%) receive warfarin as anticoagulation therapy while the remaining receive aspirin or direct oral anticoagulants.

Conclusion: Our population cohort demonstrated a high incidence of pregnancy morbidities and a similar incidence of thrombotic events compared to other population cohorts in both Asian and the European countries.

KEYWORDS:
Antiphospholipid syndrome, antiphospholipid antibodies, pregnancy morbidity, thrombosis, systemic lupus erythematosus

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by vascular thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL).[1] This condition is characterised as primary when it occurs alone and secondary when it is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE).[2]

Patients with APS can present with a variety of clinical, haematological and serological manifestations. Apart from thrombosis and obstetric morbidities, other features, also known as non-criteria manifestations of APS have been shown to be associated with APS. These features include immune thrombocytopenia and autoimmune haemolytic anaemia, livedo reticularis, Libman-Sachs endocarditis, APS nephropathy and cognitive dysfunction.[3] Although these non-criteria manifestations are not specific to primary APS, studies have suggested that their presence could potentially be associated with an increased risk of thrombosis.[4]

Although rare, another subgroup of APS patients can develop catastrophic antiphospholipid syndrome (CAPS), which is characterised by widespread thromboses with end organ damage and is associated with a significantly higher degree of mortality.[5]

Determining the prevalence of APS remains challenging due to changes in the definition of APS classification criteria, the lack of standardisation to detect aPL, differences in laboratory cutoffs and difficulties in confirming aPL positivity 12 weeks after the initial measurement. Fortunately, several new publications in the recent years have greatly improved our insights on the incidence and prevalence of APS.

In the United States, the estimated population prevalence of APS is 50 cases per 100,000 with an annual incidence of 2.1 per 100,000.[6] In the United Kingdom, the estimated population prevalence of APS is 43 per 100,000 with an annual incidence of 1.8 per 100,000.[7] In Spain, the estimated population prevalence of APS is 40 cases per 100,000.[8] In the Asian population, the estimated population prevalence of APS is six cases per 100,000 with an annual incidence of 0.75 per 100,000.[9] CAPS have been estimated to affect less than 1% of patients with APS.[10]

Observational studies have shown that aPL may be positive in as many as 13% of patients with stroke, 11% of patients with myocardial infarction and 9.5% of patients with deep vein thrombosis.[11] aPL can be present in normal healthy population as well but the data on the prevalence of aPL among healthy population is still limited. In addition, other autoantibodies such as IgA isotypes (IgA anticardiolipin antibodies and IgA anti-beta 2 glycoprotein 1 antibodies), and phosphatidylserine/prothrombin complex autoantibodies (aPS/PT), among others, have also been reported to cause APS but their clinical relevance remains controversial.[12]

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Our study aims to describe the clinical features, serological characteristics, treatment strategies and outcomes of APS patients treated at Rheumatology Unit, Hospital Pulau Pinang, Malaysia.

MATERIALS AND METHODS

This was a retrospective cross-sectional study of patients with APS treated in Rheumatology Unit, Hospital Pulau Pinang from October 2021 until October 2022.

The diagnosis of APS was made according to the Sapporo's classification criteria in 2006 where patients must fulfil at least one clinical and one laboratory criteria (Table I).[3]

Demographic data, types of APS, clinical manifestations, treatment strategies, serological features and treatment outcomes were retrieved from medical records.

Data was analysed using Statistical Package for Social Sciences Software (version 21.0). Numeric variables were expressed as mean ± standard deviation and categorical variables were expressed as numbers and percentage. Mann-Whitney test was used to compare differences between two independent groups if the distribution were not normal. $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Of the 53 adult patients with APS, eight (15.1%) were males and 45 (84.9%) were females, with a mean age of 42.4±13.9 years. Majority of the APS patients were Malays (23/53, 43.4%), followed by Chinese (17/53, 32.1%) and Indians (13/53, 24.5%). Twenty-two (41.5%) have primary APS while 31 (58.5%) have secondary APS. Out of the 31 patients with Secondary APS, 30 had SLE while the remaining one had Takayasu's arteritis. The mean age of onset of APS in was 32.6±12.4 years (Table II).

Clinical Manifestations

A total of 26 (49.1%) patients developed venous thrombosis while 30 (56.6%) had arterial thrombosis. Six (11.3%) patients developed both arterial and venous thrombosis. Of all the patients with venous thrombosis, 21 (39.6%) had deep vein thrombosis while eight (15.1%) had pulmonary embolism. Other APS patients who developed venous thrombosis had cerebral venous thrombosis (3/53, 5.7%), retinal vein thrombosis (1/53, 1.9%) and Budd-Chiari Syndrome (1/53, 1.9%). Of all patients with arterial thrombosis, 17 (32.1%) had ischaemic stroke while 7 (13.2%) had digital ischaemia. The remaining patients with arterial thrombosis had intracardiac thrombus (2/53, 3.8%), coronary artery disease (1/53, 1.9%) and small artery thromboses (1/53, 1.9%) (Table III).

Another 15 (33.3%) patients had pregnancy morbidities where four patients experienced early foetal loss and five patients experienced late foetal loss. Three patients had premature births and pre-eclampsia respectively (Table III).

Fourteen (26.4%) patients had thrombocytopenia where nine of these patients have concomitant SLE while the remaining five are patients with primary APS. Ten (18.9%) patients had autoimmune haemolytic anaemia, where nine had concomitant SLE and the remaining one was a patient with primary APS. Only one patient had valvular heart disease, APS nephropathy, epilepsy and vasculitic ulcer respectively while another two had livedo reticularis. None of our patients develop cognitive dysfunction (Table III).

Serological Characteristics

Ten (18.9%) patients tested positive for all three aPL while 17 (32.1%) patients tested positive for at least two aPL and 26 (49.1%) patients tested positive for only one of the aPL. Forty-seven (88.7%) patients tested positive for lupus anticoagulant (LA) while 27 (50.9%) patients and 16 (30.2%) patients tested positive for aCL and anti-beta 2 glycoprotein 1 antibody (B2GP1) respectively. Thirty-seven (69.8%) patients had antinuclear antibodies (ANA), of which seven were primary APS patients and 30 were secondary APS patients. Seventeen (32.1%) patients had anti-double stranded DNA (dsDNA) and all these patients were patients with SLE. All primary APS patients who tested positive for ANA tested negative for anti-dsDNA. Nine (17%) of APS patients tested positive for anti-SSa while three (5.67%), five (9.4%) and six (11.3%) tested positive for anti-SSb, anti-Sm and anti-RNP respectively. 21 (43.4%) of our APS patients had low complement levels, of which 21 were SLE patients while the remaining two patients were patients with primary APS (Table III).

Treatment Decisions

Forty-six (86.8%) patients received warfarin while 10 (18.9%) received aspirin for treatment of APS. Only two (3.8%) of our APS patients received direct oral anticoagulants (Table IV).

Follow up Duration and Treatment Outcomes

The mean follow-up duration of APS patients in our population were 13±6 years. Fifty-two (98.1%) patients are alive while one (1.9%) patient passed away due to advanced cervical carcinoma (Table IV).

Differences Among Primary and Secondary APS Patients
Demographics

In our population cohort, both primary and secondary APS patients were more prevalent among females (14.3 vs. 85.7%, 15.6 vs. 84.4%). More patients with secondary APS had an age at onset of less than 20 years of age compared to primary APS patients (18.8 vs. 4.8%). More secondary APS patients also had an age at onset of more than 50 years old compared to primary APS patients (9.4 vs. 4.8%). However, we could not demonstrate a statistical significance when comparing the prevalence of primary or secondary APS patients in relation to the age of onset (Table V).

Clinical Manifestations

In our study population, more patients with secondary APS had arthritis, rash and ulcers and AIHA. Both primary and secondary APS patients have similar incidence of thrombocytopenia, venous thrombosis, arterial thrombosis, and pregnancy morbidities (Table V).

Table I: Sapporo classification criteria for antiphospholipid syndrome.

Clinical criteria	
1. Vascular thrombosis (confirmed by imaging or histopathological studies) 2. Pregnancy morbidity	a. One of more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ. a. Three or more sequential spontaneous abortions before 10th week of gestation; or b. Unexplained foetal death of a morphologically normal foetus after 10th week of gestation; or c. Early birth before 34th week of gestation of a morphologically normal foetus due to eclampsia, severe pre-eclampsia or confirmed placental failure
Laboratory criteria	
	a. Lupus anticoagulant present in plasma, confirmed on minimally two occasions with an interval of at least 12 weeks b. Anticardiolipin-antibodies (aCL), IgG- or IgM- isotype, present in serum or plasma, with elevated titre (>99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks c. Anti-beta 2 glycoprotein-1-antibodies (B2GP1), IgG- or IgM-isotype, present in serum or plasma (with titre >99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks

Table II: Demographic data of APS patients.

Characteristics	**Value**
Mean age (years) (±SD)	42.4±13.9
Gender	
Male, n(%)	8 (15.1%)
Female, n(%)	45 (84.9%)
Ethnic	
Malay, n(%)	23 (43.4%)
Chinese, n(%)	17 (32.1%)
Indian, n(%)	13 (24.5%)
Types of APS	
Primary APS, n(%)	22 (41.5%)
Secondary APS, n(%)	31 (58.5%)
Mean age at diagnosis (years) (±SD)	32.6 ± 12.4

Serological Characteristics

While more primary APS patients tested positive for LA (95.5 vs. 83.8%, p=0.19), and more secondary APS patients tested positive for ACL (54.8 vs. 45.5%, p=0.50) and B2GP1 (35.5 vs. 22.7%, p=0.32), the differences were not statistically significant. In our population cohort, secondary APS patients with triple positivity were much higher compared to primary APS patients (19.4 vs. 18.2%, p=0.04). However, we did not observe any statistical significance when comparing patients who tested positive for only two aPL among the primary and secondary APS patients. ANA positivity was found in majority of our secondary APS patients (96.8 vs. 31.8%, p=0.002). Anti-double stranded DNA (DsDNA) was also present in significantly more secondary APS patients compared to primary APS patients. More secondary APS patients in our population tested positive for extractable nuclear antigens, namely anti-Ro, anti-La, Anti Sm and anti-RNP (Table V).

DISCUSSION

In this study, we report a retrospective observation of APS patients in Hospital Pulau Pinang, Malaysia. The mean age of APS patients in our study was below 50 years (mean age of onset of APS 32.6±12.4 years) which was similar to other population studies.6 Interestingly, the frequency of secondary APS was higher in our study population compared to primary APS. This finding was similar to another study from Singapore[13] but different compared to the European, American, French and the Euro-Phospholipid cohort.[15] A recent retrospective study from Pakistan also showed a higher incidence of primary APS compared to secondary APS in their population cohort (88 vs. 12%).[16] This may be due to a lack of awareness to screen young patients who present with thrombotic events and pregnancy morbidities in our region, leading to a lower detection rate of primary APS.

In our study population, patients with APS have a male to female ratio of 1:5.5. This finding is consistent with the fact that systemic autoimmune diseases, including SLE and APS tend to be more frequent in women.[17]

All our secondary APS patients have SLE, except for one patient who was diagnosed with Takayasu arteritis with secondary APS. The incidence of Takayasu arteritis and secondary APS remains largely unknown. To date, there has only been one case report detailing a patient who was diagnosed with Takayasu's arteritis and secondary APS.[18] It is postulated that high titres of antiphosholipid antibodies may trigger large-vessel vasculitis in secondary APS.[18] In addition to SLE, Mushtaq et al also reported cases of rheumatoid arthritis, ANCA associated vasculitis and mixed connective tissue disease being associated with secondary APS.[16]

In our retrospective study, approximately one third of our female APS patients experienced pregnancy morbidities. Another local study in Kelantan, Malaysia reported an even higher incidence of pregnancy morbidities (78.6%) among

Table III: Clinical manifestations and serological characteristics of APS patients.

Characteristics	Value
Venous thrombosis	26 (49.1)
Deep vein thrombosis	21 (39.6)
Pulmonary embolism	8 (15.1)
Cerebral venous thrombosis	3 (5.7)
Retinal vein occlusion	1 (1.9)
Budd-Chairi syndrome	1 (1.9)
Arterial thrombosis	30 (56.6)
Cerebrovascular accident	17 (32.1)
Digital ischaemia	7 (13.2)
Coronary artery disease	1 (1.9)
LV thrombus	2 (3.8)
Iliac artery thrombosis	1 (1.9)
Mesenteric artery thrombosis	1 (1.9)
Renal artery thrombosis	1 (1.9)
Arterial and venous thrombosis	6 (11.3)
Pregnancy morbidities	15 (33.3)
Early foetal loss	4 (26.7)
Late foetal loss	5 (33.3)
Early and late foetal loss	5 (33.3)
Premature birth	3 (20.0)
Pre-elcampsia/eclampsia	3 (20.0)
Valve disease	1 (1.9)
APS nephropathy	1 (1.9)
Livedo Reticularis	2 (3.8)
Cognitive dysfunction	0
Thrombocytopenia	14 (26.4)
Epilepsy	1 (1.9)
Autoimmune haemolytic anaemia	10 (18.9)
Vasculitic ulcer	1 (1.9)
Serological Characteristics	**Value, n (%)**
Lupus anticoagulant	47 (88.7)
Anti-cardiolipin antibody	27 (50.9)
Anti-beta 2 glycoprotein 1 antibody	16 (30.2)
Single positive	26 (49.1)
LA 24 (92.3)	
aCL	2 (7.7)
B2GP1	0
Double positive	17 (32.1)
LA + aCL	11 (64.7)
LA + B2GP1	2 (11.8)
aCL + B2GP1	4 (23.5)
Triple positive	10 (18.9)
Antinuclear antibody (ANA)	37 (69.8)
Anti-double stranded DNA (Anti-dsDNA)	17 (32.1)
Extractable nuclear antigen (ENA)	
Anti-SSa	9 (17)
Anti-SSb	3 (5.67)
Anti-Sm	5 (9.4)
Anti-RNP	6 (11.32)
Low complements (C3 and C4)	23 (43.4)

Table IV: Treatment and Outcomes of APS patients.

Treatment	Value, n (%)
Warfarin	46 (86.8)
Aspirin	10 (18.9)
Direct oral anticoagulants	2 (3.8)
Treatment Outcome	**Value, n (%)**
Alive	52 (98.1)
Dead	1 (1.9)

Table V: Differences in demographics, clinical manifestations and serological characteristics among primary and secondary APS patients.

	Primary APS n=22	Secondary APS n=31	p value
Demographics			
Male, n(%)	3 (14.3)	5 (15.6)	0.80
Female, n(%)	18 (85.7)	27 (84.4)	0.80
Age at onset less than 20 years old, n(%)	1 (4.8)	6 (18.8)	0.14
Age at onset more than 50 years old, n(%)	1 (4.8)	3 (9.4)	0.53
Clinical manifestations			
Arthritis, n (%)	0 (0)	11 (35.5)	0.002
Mucocutaneous – rash and ulcer, n (%)	1 (4.5)	12 (38.7)	0.004
Renal involvement, n (%)	1 (4.5)	0	0.21
Livedo reticularis, n (%)	0 (0)	2 (6.5)	0.22
AIHA, n (%)	1 (4.5)	9 (29.0)	0.02
Thrombocytopenia, n (%)	5 (22.7)	9 (29.0)	0.61
Venous thrombosis, n (%)	9 (40.9)	11 (35.5)	0.69
Arterial thrombosis, n (%)	8 (36.4)	17 (54.8)	0.18
Both venous and arterial thrombosis, n (%)	3 (13.6)	3 (9.7)	0.65
Pregnancy morbidities, n (%)	6 (27.3)	9 (29.0)	0.89
Pregnancy morbidity and thrombosis	5 (22.7)	8 (25.8)	0.79
Serological characteristics			
LA, n (%)	21 (95.5)	26 (83.8)	0.19
aCL, n (%)	10 (45.5)	17 (54.8)	0.50
B2GP1, n (%)	5 (22.7)	11 (35.5)	0.32
Double positivity, n (%)	6 (27.3)	11 (35.5)	0.66
Triple positivity, n (%)	4 (18.2)	6 (19.4)	0.04
ANA, n (%)	7 (31.8)	30 (96.8)	0.002
dsDNA, n (%)	0	17 (54.8)	0.005
Anti-SSA, n (%)	0	9 (29.0)	0.007
Anti-SSB, n (%)	0	3 (9.7)	0.15
Anti-Sm, n (%)	1 (4.5)	3 (9.7)	0.53
Anti-RNP, n (%)	0	6 (19.4)	0.04

female APS patients while a retrospective study of an Italian cohort reported a lower incidence of pregnancy morbidities among female APS patients (12.4%).[10,19] Late foetal demise was the most common obstetric manifestation in our study, similar to studies from Thailand and Japan.[20,21] Interestingly, we did not observe any difference in the incidence of pregnancy morbidities between our primary APS and secondary APS patients.

In our cohort, DVT was the major thrombotic event. DVT was the most common venous thrombotic event while cerebral infarction was the most common arterial thrombotic event. The incidence of venous thrombosis reported in our study was slightly lower compared to arterial thrombosis (49.1 vs. 56.6%). This was different from findings reported in another retrospective study of Hungarian APS patients where the incidence of venous thrombosis was higher (36.4%) compared to arterial thrombosis (33.8%).[22] Compared to the Euro-Phospholipid project, our population cohort had a similar incidence of deep vein thrombosis (39.6 vs. 38.69%) and pulmonary embolism (15.1 vs. 14.1%) but a higher incidence of ischaemic stroke (32.1 vs. 19.8%).[23]

Catastrophic APS, a rare and feared complication of APS which usually occurs in less than 1% of patients with APS was not reported in our cohort of patients.

In our cohort, LA was the most common aPL detected, followed by aCL and B-2 glycoprotein-I antibody. This was different compared to the Euro-Phospholipid Project and Pakistan cohort where aCL antibodies was the most common antibody found in their cohort of primary and secondary APS patients.[16,23] Out of the eleven patients who tested positive for both LA and aCL, five patients (45.5%) developed thrombotic events only while six patients (54.5%) developed both thrombotic events and pregnancy morbidities. Out of the four patients who tested positive for LA and B2GP1, three patients (75%) developed thrombotic events while one patient (25%) developed both thrombotic events and pregnancy morbidities. This finding indicates that the presence of LA poses a higher risk of developing thrombotic events compared to pregnancy morbidities. This is consistent with previous studies showing that the presence of LA has an odds ratio for thrombosis 5 to 16 times higher than controls.[22]

Additionally, several APS-related manifestations which were not included in the classification criteria were also found in our population cohort. In our study, APS-associated thrombocytopenia is one of the most common non-criterion manifestations of APS (26.4%) followed by AIHA (18.9%). The incidence of APS-associated thrombocytopenia in our study population was comparable to the Euro-Phospholipid project (29.6%) while our incidence of AIHA was significantly higher compared to the Euro-Phospholipid project (9.7%).23 Compared to our study population, the Singapore cohort has a higher incidence of APS-associated thrombocytopenia (49.2%) and a similar incidence of AIHA (22%).[13]

In our study cohort, only one patient (1.9%) developed epilepsy, vasculitic skin ulcer and Libman-Sacks endocarditis

respectively which was slightly lower than what was being reported from the Euro-Phospholipid project.[23] Compared to the Euro-Phospholipid project, we also had lower incidence of livedo reticularis being reported (3.8 vs. 24.1%).[23]

Interestingly, there was one patient in our population cohort that was diagnosed with Evans syndrome a few years after the diagnosis of primary APS. To date, there has only been one case report on simultaneous Evans syndrome and primary APS.[24]

APS nephropathy has previously been reported to affect approximately 2.7% of APS patients.[25] In our population cohort, only one patient (1.9%) had APS nephropathy evidenced by presence of renal artery thrombosis. However, the true incidence of renal involvement in APS is likely higher as renal biopsies are often not performed due to the use of anticoagulant therapy, thrombocytopenia, systemic hypertension and concerns of biopsy-related complications.[26] Among other features, 60% (18/30) of our APS patients with SLE also presented with lupus nephritis in our study. None of our APS patients developed catastrophic APS.

The presence of secondary APS in SLE patients has been shown to significantly affect survival and outcomes of these patients. Pons-Estel et al. demonstrated that eight-year survival of primary APS patients is 83% while patients with SLE and secondary APS had survival rates of 75%.[27] The Euro-Phospholipid Project, on the other hand, demonstrated a similar mortality rate among primary APS patients and secondary APS patients with SLE (7.1 vs. 6.8%).[23] In our cohort, only one secondary APS patient with SLE passed away after a mean follow up of 8 years due to advanced cervical carcinoma. The observed reduced mortality in our cohort can be explained by the fact that our cohort had fewer patients compared to other population cohort from other parts of the world.

A substantial number of our patients (86.8%) received warfarin while only 18.9% and 3.8% received aspirin and DOAC respectively for treatment of APS. Vitamin K antagonist (VKA) oral anticoagulants have always been the preferred pharmacological management of thrombotic APS. However, its use is accompanied by problems, such as the need for frequent blood taking for INR monitoring, drug and food interaction and teratogenicity. Novel direct oral anticoagulant (NDOAC), including direct oral thrombin inhibitor (e.g., dabigatran) and direct anti-Xa inhibitors (e.g., rivaroxaban, apixaban and edoxaban) may be effective in the prevention of thrombosis in APS patients. Cohen et al showed that rivaroxaban could be a safe and effective alternative treatment in APS patients as there was no observed difference in thrombotic events of major bleeding during the six-month follow up.[28] However, the significantly shorter half-life of DOACs may lead to a higher recurrent thrombotic risk compared to VKA. Hence, switching from VKA to DOACs in patients with poor compliance to VKA is not appropriate or recommended.[29] In our population cohort, two thrombotic APS patients who received rivaroxaban have not developed any recurrent thrombotic events.

There are some limitations to this study. Firstly, our study was a retrospective study, and the sample size was relatively smaller compared to other population cohort. Furthermore, the true prevalence of APS may be underestimated as non-criteria manifestations of APS, including autoimmune haemolytic anaemia, APS nephropathy, cognitive dysfunction, livedo reticularis and Libman-Sachs endocarditis have been shown to be associated with APS more recently.

CONCLUSION

In conclusion, antiphospholipid syndrome (APS) is a complex thromboinflammatory syndrome with various clinical manifestations. Our population cohort demonstrated a high incidence of pregnancy morbidities as well as a similar incidence of thrombotic events when compared to other population cohorts in both Asian and European countries. Most of our APS patients with thrombotic events receive warfarin. The epidemiology of APS remains limited as larger population-based studies are needed to determine the frequency of APS among different racial and ethnic groups. As the classification criteria for APS continues to evolve, more patients may be reclassified as APS patients in the future. Hence, the incidence and prevalence of APS may continue to evolve in the future.

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CONFLICT OF INTEREST

No conflict of interest declared.

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Clinical characteristics and surgical outcomes of acute acquired concomitant esotropia in a tertiary referral centre in Malaysia

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ABSTRACT

Introduction: Acute acquired concomitant esotropia (AACE) is an uncommon type of strabismus that occurs due to interruption of fusion. Limited data are available on AACE from Asian countries especially from the Southeast Asian region. We aim to describe the clinical profile and surgical outcomes of AACE patients treated in a tertiary hospital in Malaysia.

Materials and Methods: We conducted a retrospective study of 20 patients aged 3-26 years who were diagnosed with AACE and attended Hospital Universiti Sains Malaysia, Kelantan, Malaysia, between January 2020 and June 2022 with follow-up periods a minimum of 12 months. Demographic data, clinical features, neuroimaging, surgical intervention, and final ocular alignment outcomes were recorded.

Results: The mean age of onset was 9.7±6.6 years. There were equal numbers of males and females in this study. Hypermetropia (45%) was the leading refractive error. Angle of deviation of 50 PD and more was documented in 50% of the patients at distance, and 70% of the patients at near fixation. Fifty per cent had an absence of stereoacuity at presentation. Neuroimaging was performed on 13 patients (65%), and two patients had intracranial pathology. All patients underwent bilateral medial rectus recession during primary surgery. Eighteen patients (90%) experienced excessive near work-related activities for >4 hours per day, and 19 patients (95%) achieved good ocular alignment, restoration of stereoacuity and resolved diplopia after the surgical intervention.

Conclusion: The mean age of onset was 9.7±6.6 years. Almost half of our patients had uncorrected hypermetropia. Furthermore, 90% of patients had excessive near-work activities, and 95% achieved good post-surgery alignment.

KEYWORDS:
Acute acquired concomitant esotropia, angle of deviation, near-work activities, post-surgery alignment

INTRODUCTION

Acute acquired concomitant esotropia (AACE) is a rare subtype of esotropia that affects older children and adults.[1] It occurs in 0.3% of childhood strabismus.[2] It presents with sudden onset large-angle esotropia with diplopia and minimal refractive error. AACE was initially classified into three subtypes by Burian and Miller in 1958: Type 1 (Swan), which is described as sudden onset esotropia due to interrupted fusion by monocular occlusion or vision loss; Type 2 (Burian–Franceschetti), which may be caused by physical or psychological stress and is demonstrated by large-angle deviations and low degree hyperopia and Type 3 (Bielschowsky), which is associated with moderate myopia or might result from excessive near-work activities.[2,3]

AACE has been reported previously to be associated with the presence of refractive error, decompensated esophoria with progressive intermittent, horizontal or binocular diplopia that converts into constant concomitant large-angle esotropia and a history of near-work activities.[1-4] Home confinement and online classes has increased the usage of computers, smartphones and tablets during the COVID-19 pandemic, thus increasing near-work activity and reduce time spent outdoors. A few recent studies reported an increase in the incidence of acquired concomitant esotropia due to near-work activities by the application of gadgets.[5-8]

There are published studies from Asian countries such as India, China and Korea that have reported good surgical outcomes in patients with AACE with the restoration of normal binocular vision and stereopsis.[2,5-6,8-15] However, limited data are available in Southeast Asian countries except Thailand. In this study, we aim to describe the clinical profile and surgical outcomes of AACE patients treated in a tertiary hospital in Malaysia.

MATERIALS AND METHODS

This was a retrospective case series conducted among patients with AACE who were diagnosed from January 2020 to June 2022 at Hospital Universiti Sains Malaysia, which is a tertiary referral centre in Malaysia. Approval was obtained from the Human Research Ethics Committee of Universiti Sains

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Table I: Summary of clinical cases.

Number	Age of onset / Gender	Presence of diplopia	Near work activities per day	BCVA	Cycloplegic refraction	Prism cover test	Stereopsis	Strabismus surgery	Neuroimaging	Type of acquired esotropia	Final outcome at one year after surgery
1	26/F	+	8	6/6 BE	RE: plano LE: +0.50	Dcc: AET 50+16 Ncc: AET 50+16	+	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
2	17/M	+	3	6/6 BE	RE: plano LE: plano	Dsc: LET 35 Nsc: LET 35	+	First surgery: BE MR Recession, Second surgery: BE LR resection	Large Extradural Haemorrhage at Left Parietal Lobe	Type I	BE: Orthophoria
3	16/M	-	10	6/6 BE	RE: -4.25 LE: - 4.50	Dcc: AET 50 Ncc: AET 50	+	BE MR Recession	NA	Type III	BE: Orthophoria
4	15/F	+	7	6/6 BE	RE: -1.50 LE: - 0.75	Dcc: AET 30 Ncc: AET 30	-	BE MR Recession	NA	Type III	BE: Orthophoria
5	12/F	+	2	6/9 RE 6/6 LE	RE: plano LE: plano	Dsc: RET 20 Nsc: RET 16	+	BE MR Recessio	Cystic lesion at Right cerebellum	Type I	BE: Orthophoria
6	12/F	+	5	6/6 RE 6/12 LE	RE: +0.75 LE: +1.25	Dcc: RET 30 Ncc: RET 50	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
7	12/F	-	5	6/6 BE	RE: +1.25 LE: +1.00	Dcc: RET 50 Ncc: RET 50	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
8	11/M	-	10	6/7.5 BE	RE: -9.00 LE: -8.25	Dcc: RET 40 Ncc: RET 50	+	BE MR Recession	NA	Type III	BE: Orthophoria
9	9/F	+	5	6/6 BE	RE: +1.25 LE: +3.75	Dcc: LET 50+10 Ncc: LET 50+20	-	BE MR Recession	CT-scan Brain Normal	Type II	Residual: AET 45
10	8/F	-	8	6/12 BE	RE: +0.75 LE: +1.00	Dcc: LET 50 Ncc: LET 50	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
11	8/M	-	5	6/12 RE 6/9 LE	RE: +2.25 LE: +2.25	Dcc: RET 50+10 Ncc: RET 50+10	+	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
12	7/M	+	8	6/7.5 BE	RE: +3.75 LE: +1.50	Dcc: RET 30 Ncc: RET 35	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
13	7/M	-	10	6/7.5 BE	RE: -0.75 LE: -1.00	Dcc: LET 50 Ncc: LET 50+20	+	BE MR Recession	NA	Type III	BE: Orthophoria
14	6/M	-	5	6/6 BE	RE: -0.75 LE: -0.75	Dcc: AET 40 Ncc: AET 50	-	BE MR Recession	NA	Type III	BE: Orthophoria
15	6/F	-	8	6/7.5 BE	RE:-1.50 LE: -3.00	Dcc: LET 30 Ncc: LET 40	+	BE MR Recession	NA	Type III	BE: Orthophoria
16	5/F	-	10	6/6 BE	RE: +1.25 LE: +0.75	Dcc: AET 45 Ncc: AET 50	+	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
17	5/M	-	6	6/9 RE 6/12 LE	RE: -0.75 LE: -1.00	Dcc: LET 25 Ncc: LET 40	+	BE MR Recession	NA	Type III	BE: Orthophoria
18	4/F	-	5	6/6 BE	RE: +1.75 LE: +0.75	Dcc: AET 50 Ncc: AET 50	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
19	4/M	-	6	6/6 BE	RE: +0.25 LE: +0.25	Dcc: AET 50+10 Ncc: AET 50+20	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria
20	3/M	-	5	6/6 BE	RE: +1.50 LE: +1.50	Dcc: AET 50 Ncc: AET 50	-	BE MR Recession	CT-scan Brain Normal	Type II	BE: Orthophoria

BE = both eyes, RE = right eye, LE = left eye, Dcc = distance with correction, Ncc = near with correction, Dsc = distance without glasses, Nsc = near without glasses, BCVA = best corrected visual acuity, AET = alternating esotropia, MR = medial rectus, LR = lateral rectus, CT = computed tomography

Table II: Distribution of type of AACE and age group.

Type	0 to 10 years old n=12 (%)	11 to 20 years old n=7 (%)	21 to 30 years old n=1 (%)
Type I	0 (0.0)	2 (29.0)	0 (0.0)
Type II	8 (67.0)	2 (29.0)	1 (100.0)
Type III	4 (33.0)	3 (42.0)	0 (0.0)

Malaysia (USM/JEPeM/21100675). The study was conducted in accordance with the Declaration of Helsinki. All participants and their guardians provided written informed consent for their clinical records to be used in this study.

The diagnosis of AACE was based on an acute onset of concomitant esotropia for weeks or months with photographic evidence of the absence of strabismus before esotropia onset, and concomitant esodeviation with normal gaze movement. Exclusion criteria included a history of ocular surgery (except for refractive surgery), ocular trauma, accommodative spasm and accommodative esotropia (hypermetropia ≥ +2.00 dioptres) with a resolution of deviation with full hyperopic correction.

Patients were identified based on the above inclusion and exclusion criteria, and their medical records were retrieved. Medical history and demographic data, which included age, gender and onset of diplopia, were collected. Duration of near-work activities at 30cm distance including smartphone or handheld gadget usage and reading books prior to the time of onset was recorded. Duration of near-work activities of >5 hours per day was defined as excessive near work.[2]

Best-corrected visual acuity (BCVA) was documented in all cases. Stereoacuity was based on the Frisby test. Orthoptic examinations, which included ocular movement and deviation, were performed using an alternate prism cover test performed with near (33cm) and distance fixations (6m). All patients underwent a meticulous ocular examination, including a slit-lamp assessment of the anterior segment and a dilated fundus examination.

Cycloplegic refraction was performed following the administration of 1% cyclopentolate eye drops in all patients. The spherical equivalent was calculated as the sum of the dioptric power of the sphere and half of the cylinder. Hypermetropia was defined as spherical equivalent of more than +0.50 Dioptre. Myopia was defined as more myopic than -0.50 Dioptre.

Systemic examinations, including neurological examinations, were performed on all patients. Computed tomography (CT) of the brain was done in patients with emmetropia and hypermetropia who had persistent esotropia after a full correction treatment with glasses.[2,16] Details of treatments were recorded, including glasses prescription, and details of surgical intervention were also recorded. The final visual acuity (VA), ocular alignment and stereopsis were documented at 12 months postoperative period.

Categorical data are shown as frequencies and percentages. Continuous variables are presented as the mean ± standard deviation (SD) and range. Statistical analyses were performed using SPSS Statistic version 27.0 (IBM Corp, Armonk, NY, USA).

RESULTS

A total of 20 patients with AACE were included in this study. Table I summarises the clinical profiles of all patients involved in this study. Table II describes the distribution of types of AACE according to decades of life. Twelve patients (60.0%) emerged during the first decade, seven patients (35%) during the second decade and one patient (5%) presented during the third decade of life. Type I had the least involvement, observed in two patients (10%), whereas Type II was the most prevalent, seen in 11 cases (55%). Type III occurred in seven patients (35%).

There were equal numbers of males and females in our study. The mean age of AACE onset was 9.7±6.6 years. Two of them had a history of prematurity ranging from 28 to 34 weeks. There was no family history of strabismus, and 90% (18 patients) had a history of excessive near-work activities related to handheld gadgets, laptop usage or reading books.

Duration of near-work ranged from 2 to 10 hours per day, with a mean duration of 6.55±2.37 hours. The near-work activities were related to playing games and watching YouTube on smartphones or other handheld gadgets such as tablets in 10 patients (50%), online classes in five patients (25%), reading activities in two patients (10%) and excessively playing small toys in one patient (5%). Out of 20 patients, two developed esotropia due to intracranial pathology. One patient had a history of motor vehicle accidents and underwent left craniotomy and clot evacuation. The other patient had a cystic tumour in the right cerebellum.

Furthermore, 16 patients (80%) had BCVA of 6/6 to 6/9 using Snellen charts, while four patients (20%) had poorer vision with BCVA of 6/12. Seven patients (35%) had myopia ranging from -0.75 to -9.00 Dioptre, nine patients (45%) had hypermetropia ranging from +0.75 to +3.75 Dioptre, and four patients (20.0%) were emmetropic. Ten patients (50.0%) had distance deviation of 45 Prism Dioptre (PD) or less, while the other half had distance deviation more than 50 PD. Six (30.0%) had near deviation of 45 PD or less, and 14 (70.0%) had near deviation more than 50 PD.

In addition, nine patients with hypermetropia were prescribed glasses. However, esotropia persisted, and these patients were subjected to neuroimaging. None of these patients had remarkable findings. Two of patients with emmetropia had normal imaging, despite having mild headache. The remaining seven patients were myopic did not

Table III: Comparison of published studies on acute acquired concomitant esotropia in Asian countries.

Variables	Present study	Neena et al [6]	Meng et al [10]	Kim and Noh [9]	Lekskul et al [2]	Wu et al [11]	Cai et al [12]	Lee et al [8]	Chen et al [14]
Country (year)	Malaysia (2024)	India (2022)	China (2021)	Korea (2021)	Thailand (2021)	China (2020)	China (2019)	Korea (2016)	China (2015)
Sample size	20	15	51	24	30	26	45	12	47
Mean age (year) ±SD	9.7±6.6	16.8±5.7	24	25.3±8.6	19.8±18.3	22.5	19±7.3	13.33±3.3	26.6±12.2
Gender, n (%)									
Male	10 (50.0)	11 (73.3)	33 (64.7)	17 (70.8)	NA	15 (57.7)	30 (66.7)	5 (41.7)	25 (53.2)
Female	10 (50.0)	4 (26.7)	18 (35.3)	7 (29.2)	NA	11 (42.3)	15 (33.3)	7 (58.3)	22 (46.8)
Excessive near-work, n (%)									
Yes	18 (90.0)	14 (93.3)	51 (100.0)	13 (54.2)	6 (20.0)	20 (76.9)	14 (31.1)	12 (100.0)	NA
No	2 (10.0)	1 (6.7)	0 (0.0)	11 (45.8)	24 (80.0)	6 (23.1)	31 (68.9)	0 (0.0)	NA
Mean (hours)±SD	6.55±2.37	8.6	9	NA	NA	NA	NA	6.08±1.78	NA
Clinical presentation, n (%)									
Diplopia	7 (35.0)	13 (86.7)	51 (100.0)	24 (100.0)	NA	26 (100.0)	NA	9 (75.0)	43 (91.4)
Best corrected visual acuity									
6/6 – 6/9	16 (80.0)	15 (100.0)	51 (100.0)	24 (100.0)	30.0 (100.0)	26 (100.0)	45 (100.0)	12 (100.0)	NA
6/12 and worse	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Refractive Error, n (%)									
Myopia	7 (35.0)	5 (33.3)	42 (82.4)	22 (91.6)	24 (80.0)	24 (92.3)	41 (91.1)	8 (66.7)	33 (70.3)
Hypermetropia	9 (45.0)	10 (66.7)	9 (17.6)	1 (4.2)	6 (20.0)	2 (7.7)	3 (6.7)	4 (33.3)	5 (10.6)
Emmetropia	4 (20.0)	0 (0.0)	0 (0.0)	1 (4.2)	N/A	0 (0.0)	1(2.2)	0 (0.0)	9 (19.1)
Esotropia (Prism Diopter)									
Mean deviation at distance		22.73	25	33.1±10.4	28.4±12.1	46.48	40.5±19.5	27.75±11.47	NA
a) 45 PD and less	10 (50.0)	15 (100.0)	51 (10018-40.0)	NA	NA	NA	NA	12 (100.0)	11.3±3.9 (Less than 20 PD)
b) 50 PD and more	10 (50.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	0 (0.0)	40.7±14.0 (More than 20 PD)
Mean deviation at near		18.73	20	33.3±11.2	29.3±11.8	42.08	35.6±19.9	28.33±11.15	NA
a) 45 PD and less	6 (30.0)	15 (100.0)	51 (100.0)	NA	NA	NA	NA	NA	9.3±4.4 (Less than 20 PD)
b) 50 PD and more	14 (70.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	41.0±13.5 (More than 20 PD)
Stereoacuity, n (%)									
Present	10 (50.0)	13 (86.7)	N/A	18 (75.0)	NA	NA	12 (26.7)	4 (33.3)	47 (100.0)
Absent	10 (50.0)	2 (13.3)	N/A	6 (25.0)	NA	NA	NA	8 (66.7)	0 (0.0)
Neuroimaging, n (%)	13 (65.0)				13 (43.3)				
Normal	11 (84.6)	15 (100.0)	48 (94.1)	24 (100.0)	12 (92.3)	26 (100.0)	43 (95.6)	12 (100.0)	NA
Abnormal	2 (15.4)	0 (0.0)	3 (5.9)	0 (0.0)	1 (7.7)	0 (0.0)	2 (4.4)	0 (0.0)	2 (4.3)
Surgical intervention, n (%)	20 (100.0)	4 (26.7)	21 (41.2)	24 (100.0)	26 (86.7)	26 (100.0)	44 (97.8)	3 (25.0)	24 (51.1)
BE MR recession	20 (100.0)	1 (25.0)	NA	6 (25.0)	18 (69.2)	NA	4 (9.1)	3 (100.0)	7 (29.2)
Unilateral MR recession	NA	NA	NA	NA	6 (23.1)	NA	4 (9.1)	NA	NA
Unilateral MR recession and LR resection	NA	3 (75.0)	NA	18 (75.0)	2 (7.7)	NA	26 (59.1)	N/A	16 (66.7)
BE MR recession and unilateral LR resection	NA	NA	NA	NA	NA	NA	9 (20.4)	NA	NA
Unilateral LR resection	NA	NA	NA	NA	NA	NA	1 (2.3)	NA	1 (4.1)
Surgical outcome**, n (%)									
Orthophoria (Definition)	19 (95.0) 0-10	NA	NA	NA	NA	1 (3.8)	NA	3 (100.0)	NA
Residual esotropia	1 (5.0)	NA	0-25 PD	3.4±6.1*	0-8 PD	0-5 PD	0.8±1.6	NA	NA
Presence of stereoacuity, n %)	20 (100.0)	4 (100.0)	NA	24 (100.0)	26 (100.0)	NA	6 (13.6)	3 (100.0)	24 (100.0)

MR = Medial Rectus, LR = Lateral Rectus, PD = Prism Diopter, SD = Standard Deviation, NA=Not Aailable, *Mean ±SD, **based on number of patients who underwent surgical intervention

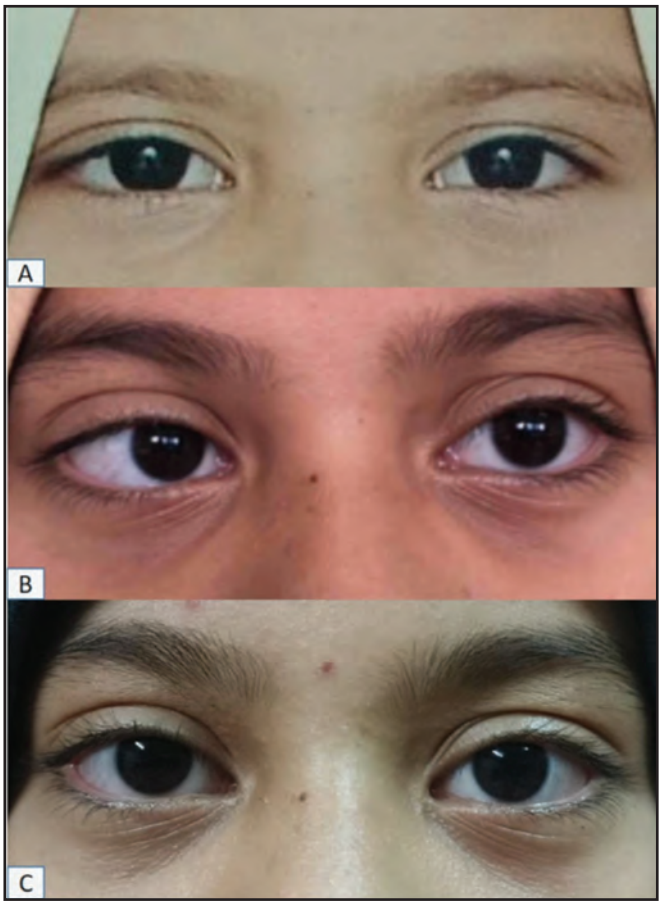

Fig. 1: A) Before onset of esotropia, B) Onset of esotropia, C) After the surgery

require imaging; none developed a neurological disease in long-term follow-up up to 12 months.

All patients had undergone bilateral medial rectus recession during primary surgery. One patient (5%) underwent a second operation: bilateral medial rectus recession followed by bilateral lateral rectus resection. Resolved diplopia, stereoacuity, and good ocular alignment were achieved in 19 patients (95%). One patient (5%) had residual esotropia during follow-up visit. Figure 1 displays photo documentation captured before the onset of esotropia, onset of esotropia and after the surgery for one of the patients recruited in this study.

DISCUSSION

There are limited reviews on AACE and its surgical outcomes in Asian countries. Neena et al from India described a report of 15 patients with AACE that was precipitated by excessive near-work during the COVID-19 home confinement.[10] There were a few studies in China by Meng et al., Wu et al., Cai et al., and Chen et al., regarding clinical characteristics, aetiologies, treatment and surgical outcomes of AACE.[10-12,14] However, the above studies have different inclusion and exclusion criteria and treatment choices compared to our study. Table III summarises published studies on AACE from Asian countries, including our study.

Recent studies have shown that AACE occurs in individuals of any age.[2,6,8-14] In our study, the mean age of onset of presentation was 9.7±6.6 which portrayed the onset of AACE at a slightly younger age compared to other published studies. This was probably due to our study was conducted during COVID-19 pandemic era where total lock downs, implementation of online classes and many children spent long hours with gadget at home. This has alerted the parents/care giver when the parents noticed sudden onset of eye deviations. In contrast, Kim and Noh reported that the mean age of onset of AACE was 25.3±8.6 in their study of 24 patients in 2021.[9] In aligning with studies conducted in Korea, Turkey and China, 50% of our patients were female, showing that there was no predominance in gender.[8,13,14] In contrast, males were predominant in other studies.[6,9,10,12]

Our study reported that 80% of our patients presented with refractive errors, where nine patients were hypermetropic and seven patients were myopic. None of the 18 patients were on corrective glasses during the initial consultation. Our results were in keeping with studies done by Neena et al. in India, where out of 15 patients with AACE, 10 were hypermetropic.[6] In contrast to our results, the patients were predominantly myopic in other published studies.[2,8-12,14] Bielschowsky claimed that uncorrected myopia led to the development of increased tonus of the medial rectus muscles and suggested that the increase in tonus can be explained by the tendency of individuals with uncorrected myopia to have excessive near-work activities, resulting in the development of esotropia.[17]

A systematic review and meta-analysis on seven large-scale population-based studies involving 23,541 children to determine the association of refractive errors and concomitant strabismus was reported in 2016 but no significant association was found between myopia and esotropia in the study.[18] On the other hand, children with myopia had a 5.23-fold increase in the risk of developing exotropia compared to those without significant ametropia. They also revealed a strong association between hypermetropia and esotropia. They found that hypermetropia starting at 2.00D to less than 3.00D imposes more than a 10-fold increase in the risk of developing concomitant esotropia. Strikingly, children with hyperopia of +5.00D or more had 218 times the risk of developing esotropia compared to children with 0.00D to less than 1.00D.[18,19]

Since the recent COVID-19 lockdown, where home confinement, school closure, and work-from-home restrictions were enforced, excessive near-work-related activities have been observed to upsurge. This has concurrently increased screen time, reduced time spent outdoors and digital eye strain.[20] Many studies have postulated that excessive smartphone use may be the underlying factor in AACE.[8,10,11,21] In our study, 18 patients were identified as excessive smartphones or handheld gadgets users whereby the average of 6.55±2.37 hours per day based on the statements of patients or their parents. Two patients admitted having reading activities at a distance of 30 cm or less for more than 5 hours per day, and one patient had a history of playing with small toys for more than 10 hours per day for 4 years. In published studies in Korea, 100%

of their patients admitted having excessive near-work activities with an average of 6-9 hours per day.[8,9] This is supported by the theory that excessive accommodation leads to an increase in medial rectus contraction, which in turn leads to the development of esotropia in AACE.

According to recent studies, AACE can affect both children and adults even when there is no corresponding neurological impairment.[8,13,15,22,23] This is in accordance with the outcomes of our study, which reported a series of patients who presented with AACE but had no other neurological or ocular abnormalities and whose examination revealed no intracranial pathology that would account for acute onset esodeviation. In the present study, 13 patients (65%) underwent neuroimaging studies. Of these, 13 patients had persistent esotropia despite full correction of hypermetropia as well as emmetropic patients, and the results were unremarkable while the other two patients had abnormalities on the neuroimaging due to intracranial bleeding post motor vehicle accident and tumour in the right cerebellum, respectively. We were selective in subjecting patients for neuroimaging, and we monitored those with myopia who did not portray any neurological deficit. These patients were not subjected to brain imaging. Montriwet et al., reported 41 patients with AACE; however, only 36 patients underwent brain and orbital neuroimaging studies. Two revealed a non-life-threatening intracranial pathology. None of their patients who did not undergo neuroimaging studies developed any neurological diseases during the follow-up period of 1.5±0.8 years.[25]

A few published studies have reported successful surgical outcomes in terms of good ocular alignment, with 100% of patients achieving postsurgical stereoacuity. Lee et al., operated on three patients, who underwent bilateral medial rectus recession, and achieved orthophoria postoperatively with a normal binocular single vision and no recurrence of esotropia,[8] which is in keeping with our study where 100% of our patients underwent bilateral medial rectus recession in their primary surgery. Also, 95% of our patients achieved good postoperative surgical outcomes in terms of fully resolved diplopia, good ocular alignment and the presence of stereopsis in 100% postoperatively. One patient had a residual of esodeviation of 45 PD in both distance and near fixation; this is due to poor compliance to glasses and persistent excessive near-work activities using handheld gadgets to play games and watching YouTube for an average of 4 hours per day postoperatively. In contrast, other authors opted for unilateral medial rectus recession and lateral rectus resection in most patients subjected to surgical intervention, and 100% regained stereopsis postoperatively with good ocular alignment.[6,9,14] We agree with the suggestion by Leskul et al., that increased recession of 0.5-1.0 mm results in good primary outcome.[2]

Our primary limitation lies in the retrospective nature of the study design. However, our strengths include successfully recruiting 20 patients within an 18-month period during the COVID-19 pandemic era at one of the country's referral centres.

CONCLUSION

Our study found that the mean age of onset of acute acquired concomitant esotropia (AACE) is slightly younger than in other published studies. There is no gender predilection. Excessive near-work activities contribute to the development of AACE with the mean hours spent being 6.55±2.37. Neuroimaging was performed in 65% of patients in view of emmetropia status and persistent esotropia despite full hypermetropic glasses correction, and 95% achieved good ocular alignment after surgery, where 100% regained stereopsis postoperatively.

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ORIGINAL ARTICLE

Efficacy of Caprini risk assessment model in predicting venous thromboembolism risks among Asian surgical patients

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ABSTRACT

Introduction: Caprini risk assessment model (RAM) has been validated in Caucasians but evidence of its suitability in Asian surgical patients is still unknown. This study aims to determine the efficacy of Caprini model in venous thromboembolism (VTE) risk assessment among Asian surgical patients.

Materials and Methods: Consecutive surgical patients with Asian ethnicities admitted to a tertiary public hospital between January 2013 and December 2014, were included. Their demographic details, VTE risk factors and scores based on Caprini RAM were recorded. Primary outcome of this study was symptomatic VTE within 90 days of hospitalisation. Fisher's exact test and Lasso regression were performed for statistical analysis.

Results: A total of 4206 patients were included in this study. Distribution of this study population by risk level was very low, 14.7%; low, 44.1%; moderate, 25.6% and high, 15.7%. The overall symptomatic VTE incidence within 90 days was 0.5%. The incidence of deep venous thrombosis (DVT), pulmonary embolism (PE) and both was 0.31%, 0.19% and 0.05% respectively. VTE incidence by risk category was very low, 0%; low, 0.16%; moderate, 0.37% and high, 2.12%. Obesity (BMI >25), history of prior major surgery, history of DVT/PE and high-risk category (scores ≥5) were significant VTE factors with odds ratio > 5.0. Following the Caprini RAM with ACCP preventive recommendations, an estimated 85% of surgical patients would need prophylaxis.

Conclusion: The overall VTE incidence among Asian surgical patients is low. Prophylaxis using Caprini RAM may subject a low incidence patient population to over utilisation of thromboprophylaxis and therefore not cost-effective when applied to Asian patients.

KEYWORDS:
Pulmonary embolism, venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) incidence among Asians is increasing. In Singapore, deep venous thrombosis (DVT) prevalence among hospitalised patients has increased significantly within a decade from 0.079% (1989-1990) to 0.453% (2002-2003).[1] Annual incidence of VTE from a Korean Health Insurance Review and Assessment Service database has also climbed from 8.83 in 2004 to 13.8 per 100,000 individuals in 2008.[2] Similarly, the annual incidence of pulmonary embolism (PE) in China has quadrupled from 0.03% (1996) to 0.14% (2006).[3] In view of this escalating incidence of VTE, a group of medical and surgical clinicians from Asian countries have formulated the Asian VTE prophylaxis guidelines published in 2012 and updated them in 2017. This group of specialists devised the prophylaxis recommendations following systematic review of Asian literature on VTE. They recommended preventive measures among surgical patients according to three risk groups: low, moderate and high. What has been lacking in these guidelines is the sufficient clinical evidence on the use of an individual risk assessment model (RAM) such as Caprini score to objectively stratify VTE risks among hospitalised patients in Asia.[4,5] An individual RAM is an important tool in VTE prophylaxis implementation strategy. Thus far, the guideline has yet to endorse any RAM due to insufficient clinical validation in Asia on the use of a RAM, which is mainly based on data from Western countries where incidences of VTE are high.

Caprini et al., first published their VTE risk assessment model in 1991. They initially categorised patients into three risk levels – low, moderate and high as per Hull's proposal.[6] Subsequently in 2005, Caprini modified his model adopting low, moderate, high and highest risk categories based on the classification in the ACCP consensus.[7] Bahl et al[8] validated the Caprini RAM retrospectively in general, vascular and urologic surgical patients, based on hospital discharge from the University of Michigan Health System (UMHS) National Surgical Quality Improvement Program in 2010.[8] Panucci et al., then validated its use in a group of moderate and high-risk plastic and reconstructive surgery patients in the United States of America.[9] Subsequent validation studies were conducted mainly among Caucasians. These validations led to the inclusion of Caprini RAM in the 9th ACCP Prevention of Thrombosis guidelines for non-orthopaedic surgical patients. The ACCP guidelines using Caprini risk stratifications recommend the following prophylaxis: early ambulation for very low risk (score 0), mechanical method in low risk (score 1-2), either pharmacological or mechanical prevention in moderate risk (score 3-4) and combined pharmacological and mechanical prophylaxis in high risk group (score ≥5).[10] Although Caprini RAM has been endorsed by the ACCP guidelines, it is not widely used among Asian

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patients. The low incidence of VTE, coupled with fear of higher bleeding risk among Asian ethnicity than Caucasian counterpart, are possible reasons of its unpopular utilisation.

To date, a few validation studies in China, Vietnam and India on Caprini RAM among hospitalised patients have been conducted. Zhou et al., validated a modified Caprini RAM with a case-control study among Chinese patients with 347 VTE inpatients and 651 randomly selected non-VTE inpatients.[11] As it was a case-control study, it did not reflect the actual VTE incidence in their hospital.[11] A study by Hanh et al., in Vietnam based on hospital discharges of close to 2.8 million surgical patients demonstrated an overall low VTE incidence of 0.11%.[12] The symptomatic VTE rates by Caprini risk level: low to moderate, 0.04%; high, 0.11% and highest, 0.27% in Hanh's study were seven to ten times lower than the incidence reported in the United States of America (low to moderate, 0.7%; high, 0.97%; highest, 1.97%).[8,12] A prospective observational study on selected patients who underwent surgeries in India however, demonstrated a high overall VTE incidence of 7.3% but these were reported only in patients with Caprini score ≥5.13 These vast heterogeneous differences in the VTE incidence between two continents and among different ethnicities pose questions on the efficacy of Caprini model to stratify VTE risk among Asian surgical patients. The aim of this study was to evaluate the efficacy of using Caprini RAM in VTE prophylaxis among multi-ethnic Asian surgical patients.

MATERIALS AND METHODS

Study Design and Patients

All elective and emergency admissions to general surgical and vascular wards in a tertiary public hospital in Serdang (a suburban town of Kuala Lumpur), Malaysia from January 2013 to December 2014 were reviewed retrospectively. Of note, Serdang hospital utilises an electronic medical record (EMR) system that includes laboratory and imaging data. Kuala Lumpur is a cosmopolitan city and has a significant migrant population - largely refugees and migrant workers besides ethnically diverse Malaysian population. Therefore, all Asian patients regardless of their nationalities were included. Data were collected from EMR of this hospital. Ethical approval was obtained from the hospital institutional ethics committee.

Caprini Risk Assessment

The VTE risk factors using 2005 Caprini RAM were recorded for each patient. The patient was categorised into risk level based on the 9th ACCP guidelines recommendations - very low risk (score 0), low risk (score 1-2), moderate risk (score 3-4) and high risk (score ≥5). There was no mandated VTE prophylaxis protocol in this hospital at the time of this study. Decision on prophylaxis prescription was made preferentially by the attending consultant. Details of VTE prophylaxis, either pharmacological, mechanical or combined methods were documented. Pharmacological prophylaxis prescribed in this hospital comprised:

i. Subcutaneous (SC) heparin 5000units twice or thrice daily,
ii. SC enoxaparin 20/40/60 mg daily
iii. SC fondaparinux 2.5mg daily
iv. Direct oral anticoagulants (DOACs) such as rivaroxaban and dabigatran.

Other DOACs such as apixaban and edoxaban were not used in this hospital during the study period.

Mechanical methods used in this hospital during the study period were class 1 graduated compressive stockings (GCS) or sequential compressive device (SCD) or both. The diagnosis of VTE was confirmed by duplex ultrasonography and/or contrast enhanced computed tomography. VTE event was recorded when it occurred within 90 days of hospital admission. Mortality occurring during hospitalisation and within 90 days after discharge was also documented.

Statistical Analysis

STATA software version 18.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Measured variables were reported as percentages for categorical data and means with standard deviation or medians with interquartile range (IQR; 25th to 75th quartile) for continuous data. Fisher's exact test was performed to determine the association between the risk factors and VTE incidence. In view of less than 10 outcome events per predictor variable, a penalised regression – Lasso regression analysis was used to calculate the odds ratio (OR) of the significantly associated risk factors for VTE incidence. Age and VTE prophylaxis were selected as potential confounding factors of VTE risk in the analysis. Variables with crude OR ≥2.0 and p-value <0.2 in the initial univariate analysis were included in the subsequent multivariate Lasso regression. OR of each Caprini risk level was also determined. Factors with p-value <0.05 (95% confidence interval, CI) were considered statistically significant.

RESULTS

A total of 4206 patients admitted to the surgical ward were included. The median age was 47 years old (IQR: 30-62). Majority of these patients, 2497/4206 (59.4%) were males. Malays were the dominant ethnic group in this study population, 2359/4206 (56.1%), followed by Chinese, 922/4206 (21.9%); Indians, 566/4206 (13.5%); Aborigines 52/4206 (1.2%) and other Asians comprised mainly immigrant workers, refugees and temporary visitors from Indonesia, Myanmar and South Asia, 307/4206 (7.3%). Median length of stay in the hospital was 2 days (IQR: 1 – 5). The overall symptomatic VTE incidence in this two-year study was 21/4206 (0.5%). Incidence of DVT, PE and both within 90 days of hospital admission was 12/4206 (0.28%), 7/4206 (0.17%) and 2/4206 (0.05%) respectively. Among the VTE cases, 18/21 patients did not undergo major surgery.

VTE prophylaxis was administered in 279/4206 (6.6%) patients during their hospital admissions. None had extended VTE prophylaxis upon discharge. A hundred and sixty-nine patients received pharmacological prophylaxis while 168 patients had mechanical measures. About 21%, 58/279 patients had combined pharmacological and mechanical therapy. Enoxaparin was the commonest pharmacological prophylaxis with 110/169 (65.1%) patients, followed by fondaparinux, 36/169 (21.3%) and low dose unfractionated heparin, 22/169 (13.0%). Only one patient had DOAC for prophylaxis. Of those who received mechanical prophylaxis, 153/168 (91.1%) patients had GCS alone, 8/168 (4.7%) SCD alone and 7/168 (4.2%) GCS and SCD. About 65% of patients who received VTE prophylaxis

had major surgery with one of them developed VTE. Despite prophylaxis, 10/279 patients developed VTE.

Overall mortality rate during hospitalisation and within 90 days after discharge was 184/4206 (4.4%). Two deceased had underlying pulmonary embolism, where causes of deaths were reported as metastatic malignancies and sepsis. Five deaths were unknown.

The following risk factors were not identified in this cohort of patients:
i. Positive factor V Leiden
ii. Elevated serum homocysteine
iii. Heparin-induced thrombocytopenia
iv. Elevated anti-cardiolipin
v. Family history of thrombosis
vi. Positive prothrombin 20210A

One patient with congenital thrombophilia developed VTE during hospitalisation. As this study comprised surgical patients only, primary thrombophilia was not routinely investigated unless there was relevant history of unprovoked thrombosis. Table I showed VTE incidence percentage and its association with each factor of the Caprini RAM.

Current swollen leg, varicose veins, obesity (BMI >25), serious lung disease including pneumonia (< 1 month), history of prior major surgery (<1 month) and history of DVT/ PE had crude OR ≥2.0 and p-value <0.2 in the initial univariate regression analysis. After adjusted multivariate regression analysis, obesity, history of prior major surgery and history of DVT/PE were statistically significant VTE predictors with OR ≥ 10.0 (p<0.05) Table II.

There were 617/4206 (14.7%) patients categorised in very low, 1854/4206 (44.1%) low risk, 1076/4206 (25.6%) moderate risk and 659/4206 (15.7%) in high-risk groups. The high-risk category was further stratified as high risk with score 5 to 6, 435/4206 (10.3%); higher (7-8), 135/4206 (3.2%) and highest (≥9), 89/4206 (2.1%). VTE prophylaxis received in each risk level was as followed: very low, 0.5%; low, 1.6%; moderate, 7.2%; high, 20.5%; higher, 31.9% and highest, 40.4%. Incidence of VTE by risk level was very low, 0%; low, 3/1854 (0.16%); moderate, 4/1076 (0.37%); high, 10/435 (2.30%); higher, 3/135 (2.22%) and highest, 1/89 (1.12%) Figure 1.

Only high risk (≥ 5) category was identified as a statistically significant risk predictor of VTE (OR 5.18, p = 0.018). Patients with score 5-6, in particular, had statistically significant OR = 3.82 of VTE incidence (p=0.015) Table III.

DISCUSSION

Asia is a diverse continent with multi-ethnicities and different socioeconomic status. Many of the epidemiological VTE studies were conducted among East Asian population, mainly from developed countries such as Korea, Taiwan, Hong Kong and Singapore. They reported a population-wide annual VTE incidence of 8 to 20 per 100,000 persons, eight times lower than the incidence reported in Caucasians, 71 to 117 per 100,000 persons.[2,14-18] A recent meta-analysis of hospital registries in Asia demonstrated that the VTE incidence ranged between 11 and 88 cases per 10,000 admissions. These incidences were still low, only 20% of that recorded in the western countries.19 Epidemiological studies on VTE incidence is still lacking in developing countries such as Malaysia and its Southeast Asian counterparts. This study demonstrated an overall low incidence of symptomatic VTE among hospitalised surgical patients, 0.5%. The incidence reported in this study population was consistent with that reported among surgical patients in most Asian countries, 0.11 to 0.85%.[12,19] In a survey conducted in 2010 among Asian specialists, only half of the respondents practiced routine VTE prophylaxis. Most of them cited low VTE incidence in Asia as the commonest reason for not practicing VTE prophylaxis routinely. Other reasons included costs and bleeding risk.[20] However, there is still a contention in the actual incidence of VTE among hospitalised patients. It is arguable that the possible reasons for the low incidence of VTE are under-reporting with lack of awareness among clinicians, limited medical resources to make diagnosis and low post-mortem rates.[21]

The results of this study showed that obesity, past history of major surgery (less than a month) and history of DVT/PE were significant risk factors of VTE (OR >2.0). These results were similar to the literature in western countries. Anderson, Spencer and Bahl reported that major surgery, and previous DVT/PE were significant risk factors with odds ratio of more than two.[8,16,17] While obesity was a marginal risk factor in the Western population, it was a significant risk factor with OR >2.0 in our cohort and study by Zhou et al.[11,16] This could be explained by a higher VTE/obesity ratio, 2/47 (4.3%) in this study than the ratio, 33/2030 (1.63%) in the Bahl's study.[8,11] Although major surgery during hospitalisation was not significantly associated with VTE in this study, patients with history of major surgery (less than a month) were 14 times at risk of VTE. This could imply two possibilities: patients who developed complications requiring multiple surgeries and/ or patients discharged without extended VTE prophylaxis after major surgeries were at high risk of VTE.

There were several differences in the reported VTE risk characteristics between this study population and the American study by Bahl et al.[8] Patients in this study were relatively younger with 73% of them aged ≤60 years, similar to a study in India (82%),[13] as compared to 59% in Bahl's study.[8] A large number of patients in Bahl's study underwent major surgery, 88.2% as opposed to 31.4% in this study.[8] Malignancy rate in this study population was 10.2%, three times lower than that among patients in Bahl's study (35%).8 There was no reported Factor V Leiden and positive prothrombin 20210A in this cohort of patients, a similar finding in the Chinese cohort by Zhou et al.[11] In contrast, there was a significant percentage of patients with these factors, 0.56% in the study by Bahl et al.[8] The rarity of Factor V Leiden and prothrombin 20210A among Asians in the literature with the exception of Indian population, supported this study finding. Prevalence of Factor V Leiden among young Indians with unprovoked DVT was reported at 9.1%.[22,23] The characteristic differences of these risk factors (elderly patients, obesity, major surgery, rate of trauma, malignancy and Factor V Leiden, prothrombin 20210A)

Table I: Distribution of VTE incidence in each risk factor and its association using Fisher's exact test.

Risk factors	VTE/N (%)	P
Age 41 – 60 (Y)	10/1316 (0.8)	0.058
Swollen Leg (Current)	3/57 (5.3)	<0.001*
Varicose Veins	2/32 (6.3)	0.012*
Obesity (BMI>25)	2/47 (4.3)	0.023*
minor Surgery Planned	1/730 (0.1)	0.156
Sepsis (<1 Month)	3/148 (2.0)	0.040*
Serious Lung Disease Including Pneumonia (< 1 Month)	3/79 (3.8)	0.008*
Oral Contraceptive Pills or Hormone Replacement Therapy	1/17 (5.8)	0.085
Pregnancy Or Postpartum (<1 Month)	1/33 (3.0)	0.159
History Of Unexplained Stillborn, Recurrent Spontaneous Abortion (≥3), Premature Birth with Toxaemia Or Growth-Restricted Infant	0/4 (0)	-
Acute Myocardial Infarction	0/27 (0)	-
Congestive Cardiac Failure (< 1 Month)	0/36 (0)	-
History Of Inflammatory Bowel Disease	0/9 (0)	-
History Of Prior Major Surgery (<1 Month)	1/21 (4.7)	0.023*
Chronic Obstructive Pulmonary Disease (COPD)	0/43 (0)	-
Age 61 To 74 Years	9/820 (1.1)	0.025*
Malignancy (Present/Previous)	7/429 (1.6)	0.005*
Laparoscopic Surgery (>45 Minutes)	0/174 (0)	-
Patient Confined to Bed (>72 Hours)	5/267 (1.9)	0.010*
immobilising Plaster Cast (<1 Month)	0/10 (0)	-
Central Venous Access	1/123 (0.8)	0.480
Major Surgery (>45 Minutes)	3/1320 (0.2)	0.250
Age ≥75 Years	0/323 (0)	-
History Of DVT/PE	7/17 (41.2)	<0.001*
Positive Lupus Anticoagulant	1/2 (50.0)	0.010*
Other Congenital/Acquired Thrombophilia	1/1 (100)	-
Stroke (<1 Month)	0/33 (0)	-
Elective Major Lower Extremity Arthroplasty	0/1 (0)	-
Hip, Pelvis or Leg Fracture	0/31 (0)	-
Acute Spinal Cord Injury or Paralysis (<1 Month)	0/7 (0)	-
Multiple Trauma (<1 Month)	1/97 (1.0)	0.402

BMI = Body mass index, n = Number of patients in each factor, *p<0.05

Table II: Caprini RAM risk factors with crude and adjusted odds ratio for VTE.

Risk factors	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Swollen leg (current)	8.69 (2.34-32.32)	0.001	4.05 (0.76-21.49)	0.101
Varicose veins	5.88 (1.33-26.00)	0.020	5.71 (0.86-37.71)	0.071
Obesity (BMI >25)	12.02 (2.68-53.93)	0.001	12.68 (2.35-68.33)	0.003
Sepsis (<1 month)	1.86 (0.45-7.76)	0.392	-	-
Serious lung disease including pneumonia (<1 month)	3.44 (0.99-11.88)	0.051	2.47 (0.53-1.37)	0.247
History of prior major surgery (<1 month)	7.62 (1.06-54.72)	0.043	13.94 (1.67-116.29)	0.015
Age 61-74 years	1.71 (0.70-4.18)	0.240	-	-
Malignancy (present/previous)	1.68 (0.51-5.55)	0.393	-	-
Patient confined to bed (>72 hours)	1.47 (0.39-5.52)	0.567	-	-
History of DVT/PE	167.23 (48.73-573.81)	<0.001	188.27 (52.12-680.09)	<0.001
OR = Odds ratio				

possibly accounted for a low incidence of VTE in this study cohort.

Comparing VTE incidence by risk score, Bahl reported 0.7% VTE incidence in patients with score ≤2, which was seven times higher compared to 3/2471 (0.1%) incidence in this study population.[8] VTE incidence in moderate risk (score 3-4) of this study population was 4/1076 (0.4%) half of that in the Bahl's study of similar score. This study demonstrated a high VTE incidence rate, 14/659 (2.1%) and a statistically significant OR of 5.18 in patients with score ≥ 5. However, when we further categorised the score of ≥5 into three different levels: 5-6, 7-8 and ≥9, the VTE incidence showed a downtrend as the score increased in this study. This result was contradictory to most studies, in which the incidence of VTE was significantly higher at score ≥7.13,[24] This could be explained by the relatively higher VTE prophylaxis rate, 32 to 40% in patients of this study with score ≥7 than those with score 5-6 (21%), resulting in a decreased VTE incidence.

More than half, 11/21 patients of this study who developed VTE within 90 days of hospitalisation did not received prophylaxis. In spite of prophylaxis, VTE occurred substantially in 10/279 (3.6%) patients implying suboptimal or ineffective preventive measures. About 85% (18/21) of the

Table III: Caprini RAM risk levels with adjusted odds ratio for VTE.

Risks	Adjusted OR (95% CI)	p
Low (1-2)	0.44 (0.11-1.73)	0.241
Moderate (3-4)	0.54 (0.18-1.69)	0.293
High (≥5)	5.18 (1.33-20.19)	0.018
5 to 6	3.82 (1.30-11.28)	0.015
7 to 8	1.67 (0.41-6.82)	0.478
>8	0.50 (0.06-4.10)	0.518

VTE cases occurred in patients who did not undergo major surgery. While it is a routine practice of VTE prophylaxis prescription in patients undergoing major surgeries, the remaining surgical patients are often not assessed of their VTE risks. Many factors such as varicose veins, obesity, sepsis, serious lung disease, malignancy, immobility and history of DVT/PE are commonly neglected as risk of VTE during hospitalisation. This supports the important role of individual risk assessment to identify high VTE risk hospitalised patients even if they do not undergo surgical procedures. This, in turn, would ensure optimal VTE prophylaxis to reduce its risk among hospitalised surgical patients.

There are two aspects of Caprini RAM: the score for each risk level and its recommended prophylaxis according to ACCP guidelines. Most studies demonstrated that the risk of VTE was higher with increasing score.[8,11-13] VTE incidence in this study of low and moderate risk levels were much lower than the incidence in the equivalent risk levels in Caucasian studies.8 In addition, VTE incidence was only found in those patients with score ≥ 5 in prospective studies by Song et al., and Bilgi et al.[13,24] About 85% of patients in this study with score ≥1 would need VTE prophylaxis when adhering to the prophylactic recommendations by the Caprini RAM. Therefore, it is not effective to apply Caprini RAM recommendation to start prophylaxis at score ≥1 in this study population when VTE incidence is low.[10]

Despite institutional prophylactic strategy using Caprini RAM in 2005 at the University of Michigan, they could only achieve 25 to 27% VTE prophylaxis rate among those patients at score ≥5.8 They were able to achieve 95 to 97% compliance rate only after a decade of Caprini RAM implementation with various measures, including EMR and a system hard stop at the University of Michigan.[25] Implementation of Caprini RAM as VTE risk stratification will be a challenge in Asia because most hospitals, particularly in South and South East Asian countries, have no EMR facility. VTE risk assessment using Caprini model with 39 factors for each patient in this continent will eventually lead to non-compliance as it is tedious and time-consuming using paper record.

With a low incidence of VTE in this cohort of surgical patients and different risk characteristics, the use of Caprini RAM may lead to over-prescription of VTE prophylaxis. In addition, the issue of bleeding risk has not been adequately addressed. There have been reports in the past of high bleeding risk after pharmacological prophylaxis, 7.3 to 13.6% among Asians.[26-29] Japanese studies demonstrate equal efficacy of a lower enoxaparin dose in VTE prophylaxis and advocate use of pharmacological measure strictly in higher risk groups.[28,29]

Based on these two factors: low VTE incidence and different bleeding profile, we need to modify Caprini RAM based on local risk factors and VTE incidence to improve its efficacy and acceptability in this community. We propose modification of Caprini RAM into three risk categories according to the Asian VTE guidelines prophylactic recommendation: low (≤2; early ambulation), moderate (3-4; mechanical or pharmacological therapy) and high (≥5; combined therapy).[4]

There are many criteria and weightage used in RAM. Some of these risks are neither inherent nor common in Asian patients, such as Factor V Leiden and positive prothrombin 20210A. Having many criteria based on types of surgery and procedures are also cumbersome in individual risk assessment. An elaborate risk score is no doubt more specific in estimating the risk but in a busy clinical setting, it becomes a daunting task for the health care worker who does the risk assessment. To simplify RAM, we recommend reduction in the number of risks: remove medical patient currently at bed rest, incorporate laparoscopic and arthroscopic surgery into single factor - major surgery, group Factor V Leiden, elevated serum homocysteine, positive prothrombin 20210A, positive lupus anticoagulant, elevated anticardiolipin antibodies and other congenital or acquired thrombophilia as single factor - thrombophilia, and distribute age into two group (age 41-60 and age >60). Using this modified RAM that caters to our population, we would be able to pragmatically implement VTE prophylaxis among Asian patients.

There were several limitations in this study. Risk factors were reported based on documentation in the medical notes, thus, substantial number of factors could be missing in the records. Panunucci et al., demonstrated that face-to-face interaction provided better accuracy in VTE risk stratification than EMR review.30 As this was a retrospective study, the incidence of VTE could be underreported. Additionally, we only captured the symptomatic VTE based on symptoms recorded in the EMR and imaging evidence. The incidence could have been higher if routine screening for VTE was done, as part of a prospective study. Lack of post-mortem for sudden deaths due to a local culture of autopsy avoidance in order to allow early release of the deceased for rituals and burial, unless there was medico-legality involvement, could contribute to the low VTE incidence. A proportion of deaths due to VTE might be missed, evidenced by a substantial percentage of deaths in this study with unknown causes after hospital discharge. Another possibility of unrecorded VTE incidence in this study was that some discharged patients could have sought treatment elsewhere.

Nevertheless, this study provides a retrospective VTE risk evaluation in Asian surgical patients as reference for future prospective validation studies of VTE RAM in this continent.

CONCLUSIONS

Venous thromboembolism (VTE) incidence among Asian surgical patients is low. Only groups with risk scores ≥ 5 significantly predicts VTE risk. Using Caprini risk assessment model (RAM) and its ACCP recommended preventive measures may be an overutilisation of VTE prophylaxis in this low-risk population and may not be cost-effective. Therefore, a modified individual RAM that caters to Asian population is needed as an important tool for implementation of an effective VTE prophylactic strategy.

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ORIGINAL ARTICLE

Conventional surgery in colon cancer with comparison to complete mesocolic excision and central vascular ligation: initial experience in a tertiary centre

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ABSTRACT

Introduction: The complete mesocolic excision (CME) and central vascular ligation (CVL) is an advanced surgical technique used to treat colon cancer. It combines the removal of the affected portion of the colon and surrounding lymph nodes with an improved method of controlling the vascular supply to the tumour.

Materials and Methods: A retrospective study of patients with colon cancer underwent right hemicolectomy (either CME and CVL or conventional method) were operated by colorectal surgeons in a tertiary centre in Kuala Lumpur from 2018 to 2020. We review the data to compare the oncological, pathological and surgical outcomes of both techniques. Categorical variables were presented as frequencies and percentages. Continuous variables were compared using an independent t-test or Mann-Whitney Rank U test. The chi-square test was used to determine the association between categorical variables and mortality. Statistical analysis was conducted with IBM SPSS Statistics 25.0, and statistical significance was set at p<0.05.

Results: A total of 30 patients (CME and CVL=15 or conventional colectomies=15) were included in this study with mean age of 65 years. There was no statistical difference between the mean age of the two groups (p=0.355). Most of the patients were Malays (46.7%) followed by Chinese (43.3 %) and Indians (10.0%). The mean (SD) = 19 (9) number of lymph nodes harvested is more in CME and CVL groups which however is not statistically significant compared to the mean (SD) = 16 (9), number of lymph nodes in conventional colectomies. The duration of surgery is longer in CME and CVL groups (214 minutes) compared to conventional colectomies (188 minutes) but with no significant statistical difference. Most of the perioperative complications were similar in both groups with no significant statistical differences.

Conclusion: CME and CVL are not inferior to conventional surgery in colon surgery in a tertiary centre. It should be considered since the advantages such as lymph node yield and median recurrence free survival are better with similar perioperative morbidity.

KEYWORDS:
Colectomy, colon cancer, large intestine

INTRODUCTION

Colon cancer is the second most common cancer in Malaysia with an overall of 21.3 cases per 100,000 population from 2008 until 2013.[1] Management of colon cancer has revolutionised over the past 30 years. Surgical treatment with conventional colectomy is considered the standard of care in the management of colon cancer. Conventional colectomy involves the removal of the affected portion of the colon, along with the mesentery containing surrounding lymph nodes and the named artery.[2] The ends of the remaining colon are then anastomosed, to restore the normal flow of intestinal contents.

There are new concepts popularised by Hohenberger since 2009, termed complete mesocolic excision (CME) and central vascular ligation (CVL).[2-22] This is an advanced surgical technique used to treat colon cancer. It combines the removal of the affected portion of the colon and surrounding lymph nodes with an improved method of controlling the vascular supply to the tumour. During CME, the entire mesentery of the colon is carefully freed up, allowing the surgeon to visualise the tumour better and the surrounding vessels.[3] The central vessels of the tumour are then identified and ligated or tied off to reduce the tumour's blood supply and decrease the risk of recurrence.[4,6,7,14-18]

Compared to conventional colon surgery, CME and CVL offer several advantages. Removing the entire mesentery significantly decreases the risk of cancer recurrence.[5,7,10] The improved visualisation of the tumour and its surrounding vessels allows for a more precise surgical resection, reducing the risk of incomplete resection and potential cancer recurrence. This technique however is technically more challenging compared to conventional. The technique is still not popular among colorectal surgeons in Malaysia. Here we performed a retrospective review comparing the CME and CVL technique and conventional colectomies in a tertiary centre in Kuala Lumpur. This review aims to assess the overall survival and perioperative morbidity among patients

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Table I: Distribution of study participants according to demographic characteristics (N=30)

		Total (n=30)	CME and CVL group (n=15)	Conventional group (n=15)	p-value
Age (years)	Mean (SD)	65.7 (11.8)	67.7 (12.2)	63.7 (11.5)	0.355
Sex	Male	18 (60.0)	9 (60.0)	9 (60.0)	1.000
	Female	12 (40.0)	6 (40.0)	6 (40.0)	
Ethnicity	Malay	14 (46.7)	5 (33.3)	9 (60.0)	0.200
	Chinese	13 (43.3)	9 (60.0)	4 (26.7)	
	Indian	3 (10.0)	1 (6.7)	2 (13.3)	

Table II: Comparison of factors between study groups (N = 30)

		Total (n=30)	CME and CVL group (n=15)	Conventional group (n=15)	p-value
Site of tumour	Ascending colon	4 (13.3)	3 (20.0)	1 (6.7)	0.309
	Caecal tumour	15 (50.0)	9 (60.0)	6 (40.0)	
	Transverse colon	5 (16.7)	1 (6.7)	4 (26.7)	
	Hepatic flexure	2 (6.7)	0 (0.0)	2 (13.3)	
	Splenic flexure	4 (13.3)	2 (13.3)	2 (13.3)	
Surgical procedure	Open	15 (50.0)	9 (60.0)	6 (40.0)	0.489
	laparoscopic converted open	4 (13.3)	1 (6.7)	3 (20.0)	
	laparoscopic	11 (36.7)	5 (33.3)	6 (40.0)	
Surgery type	Elective	13 (43.3)	9 (60.0)	4 (26.7)	0.065
	Emergency	17 (56.7)	6 (40.0)	11 (73.3)	
T staging	T1	1 (3.3)	1 (6.7)	0 (0.0)	0.192
	T2	3 (10.0)	1 (6.7)	2 (13.3)	
	T3	22 (73.3)	9 (60.0)	13 (86.7)	
	T4a	1 (3.3)	1 (6.7)	0 (0.0)	
	T4b	3 (10.0)	3 (20.0)	0 (0.0)	
N staging	0	18 (60.0)	10 (66.7)	8 (53.3)	0.304
	1	9 (30.0)	5 (33.3)	4 (26.7)	
	2	3 (10.0)	0 (0.0)	3 (20.0)	
METS	Yes	27 (90.0)	13 (86.7)	14 (93.3)	1.000
	No	3 (10.0)	2 (13.3)	1 (6.7)	
Differentiation	Poorly	3 (10.0)	2 (13.3)	1 (6.7)	0.063
	Moderately	17 (56.7)	8 (53.3)	9 (60.0)	
	Well	6 (20.0)	1 (6.7)	5 (33.3)	
	Mucinous	4 (13.3)	4 (26.7)	0 (0.0)	
Surgery duration (min)			214 (57.1)	187.9 (68.0)	0.262
Number of lymph nodes			19 (9)	16 (9)	0.197
Surgical complication					
Anastomotic leak	Yes	4 (13.3)	3 (20.0)	1 (6.7)	0.598
	No	26 (86.7)	12 (80.0)	14 (93.3)	
Sepsis	Yes	3 (10.0)	2 (13.3)	1 (6.7)	1.000
	No	27 (90.0)	13 (86.7)	14 (93.3)	
Lymph fistula	Yes	1 (3.3)	1 (6.7)	0 (0.0)	1.000
	No	29 (96.7)	14 (93.3)	15 (100.0)	
Acute urinary retention	Yes	2 (6.7)	0 (0.0)	2 (13.3)	0.483
	No	28 (93.3)	15 (100.0)	13 (86.7)	
Hematoma	Yes	2 (6.7)	2 (13.3)	0 (0.0)	0.483
	No	28 (93.3)	15 (86.7)	15 (100.0)	
Surgical site infection	Yes	6 (20.0)	3 (20.0)	3 (20.0)	1.000
	No	24 (80.00	12 (80.0)	12 (80.0)	
Non-surgical complication					
Cardiac complication	Yes	3 (10.0)	1 (6.7)	2 (13.3)	1.000
	No	27 (90.0)	14 (93.3)	13 (86.7)	
Renal failure	Yes	2 (6.7)	2 (13.3)	0 (0.0)	0.483
	No	28 (93.3)	13 (86.7)	15 (100.0)	
Local recurrence	Yes	10 (33.3)	6 (40.0)	4 (26.7)	0.439
	No	20 (66.7)	9 (60.0)	11 (73.3)	
Recurrence-free (months)	Median (IQR)	36.0 (24.0)	24.0 (24.0)	36.0 (24.0)	0.511
Stage	1	1 (3.3)	0 (0.0)	1 (6.7)	0.471
	2	17 (56.7)	10 (66.7)	7 (46.7)	
	3	9 (30.0)	3 (20.0)	6 (40.0)	
	4	3 (10.0)	2 (13.3)	1 (6.7)	
Overall survival (years)	0	1 (3.3)	1 (6.7)	0 (0.0)	0.541
	1	2 (6.7)	2 (13.3)	0 (0.0)	
	2	9 (30.0)	5 (33.3)	4 (26.7)	
	3	8 (26.7)	3 (20.0)	5 (33.3)	
	4	10 (33.3)	4 (26.7)	6 (40.0)	

undergoing CME and CVL as compared to conventional surgery in colon cancer patients.

MATERIALS AND METHODS

We retrospectively reviewed data from 2018 to 2020 on patients with colon cancer who have undergone CME and CVL, or conventional colectomies technique in a tertiary centre in Kuala Lumpur. Colectomies performed for benign conditions such as diverticulitis, inflammatory bowel disease and suspicious malignant polyps with high-grade dysplasia were excluded. Clinical data such as age, gender, site of tumour, surgical procedure and type of surgery, and histopathology data such as tumour grade and stage as well as morbidity, mortality and overall survival were included in the analysis. The clinical and histopathological characteristics are presented in Tables I and II. A total of 30 patients underwent right hemicolectomies either by CME and CVL or conventional colectomies techniques. The operation was performed either by laparoscopic or open surgery.

Descriptive statistics were used to describe the study population. The normality of continuous data distribution was determined using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean and standard deviation, while the median and interquartile range were used to describe variables with skewed distribution. Categorical variables were presented as frequencies and percentages. Bivariate analysis was performed to compare categorical variables with mortality. Continuous variables with normal distribution were compared using an independent t-test, while skewed variables were compared using the Mann-Whitney Rank U test. The chi-square test was used to determine the association between categorical variables and mortality. Fisher's exact test was used when the chi-square test assumption was violated (>20% cells with an expected value of 5 or less). Statistical analysis was conducted with IBM SPSS Statistics 25.0, and statistical significance was set at $p<0.05$.

RESULTS

A total of 30 patients' data who had undergone right hemicolectomies either by CME and CVL (n=15) or conventional colectomies (n=15) from 2018 to 2020 were retrieved for review. The mean age of the study population was 65.7 years (Standard Deviation, SD=11.8). There was no statistical difference between the mean age of the two groups (p=0.355). There were 18 males and 12 female patients in the study. The distribution of the patients according to sex was equal between groups. Most of the patients were Malays (46.7%) followed by Chinese (43.3 %) and Indians (10.0%). (Table I)

The most common site of tumours were in the caecum about 50.0%, followed by transverse colon (16.7%), ascending colon and splenic flexure (13.3%), and hepatic flexure (6.7%). The surgeries performed were mostly open surgery in both groups (CME and CVL group = 60%; conventional group = 67%). There were six patients with well differentiated tumour, 17 were moderate differentiation and 3 were poorly differentiation. There were no statistically differences among the two groups. The mean number of lymph nodes harvested is more in CME and CVL group (n=19) however it is not statistically significant compared to the conventional colectomies (n=16). The duration of surgery is longer in CME and CVL groups (n=214) compared to conventional colectomies (n=188) but with no significant statistical difference. The surgical margin for all specimens was negative. Most of the perioperative complications were similar in both groups with no significant statistical differences. (Table II)

DISCUSSION

CME and CVL surgery are still relatively a new technique with results showing a reduced risk of local recurrence (6.5 vs. 3.6%) and an improved 5-year survival rate (89.1 vs. 82.1%) compared with conventional techniques. It achieves maximal lymph node yield which therefore offers optimised oncological results.[2,4-22] This is proven as in our cohort, despite the insignificant statistical difference, the mean number of harvested lymph nodes is more in the CME and CVL groups than in the conventional groups.

As mentioned earlier, the desired endpoint of CME and CVL surgery is better local control and survival. Its technique follows the same principle as total mesorectal excision with a similar rationale but is applied in the area of colon surgery.[2,4,14,16] The principal is radical which hypothesises that tumour cells metastasise along their lymphatics but within the confines of the mesocolic fascia.[3,4-9] By removing the tumour and its mesentery with an intact mesocolic fascia, the dissemination of tumour cells is limited. Since the lymphatic drainage of the colon follows closely with its arterial supply, ligation of feeding vessels at their origin maximises the harvest of lymph nodes.[2,4] On the contrary, surgery performed in the non-anatomical plane results in the disruption of the mesocolic fascia and causes spillage of tumour cells, potentially increasing the risk of poorer oncological outcomes.[4,9]

In their study, Abdelkhalek et al., have highlighted the importance of CME and CVL surgery in terms of the amount of tissue removed around the tumour and the likelihood of tumour resection in a mesocolic plane.[5] While a small comparative series does not provide enough data to confirm the absolute benefit of the procedure to patients, it does draw attention to the potential value of mesocolic dissection, surgical plane and lymph node yield.

The research of Kim et al., suggests that the surgeon and pathologist can affect lymph node yields, potentially leading to biased outcomes.[2] However, the median node yield in Leeds was still above the United Kingdom's minimum standard, as was the recognition of extramural vascular invasion, which can be used to measure the quality of pathology.[17] The difference in lymph node yields for all resections and those for both right and left sides is too great to be accounted for by chance and is likely due to a larger quantity of tissue removed both longitudinally and centrally.[5,8,9] This is backed up by the strong correlations between longer lengths and areas and higher lymph node yields. Additionally, the amount of negative lymph nodes increased in CME and CVL surgery, which is linked to improved survival in both lymph node-negative cases and stage III disease.[2,4,5-12]

These results are in congruence with Abdelkhalek et al., who suggested that CME and CVL surgery may present the greatest benefit to patients with stage III disease.[5] This is due to the possibility that it could convert what would otherwise be a Dukes C2 case to a Dukes C1 case through downstaging. Furthermore, the plane of surgery has also been seen to be a major factor in the overall survival of patients with stage III disease. Leed's research has revealed that those with potentially curative stage III disease who have their surgery performed in the mesocolic plane have a 5-year overall survival rate of 58%, as opposed to 35%, if the surgery is done in the muscular propria plane.[2,4,14]

Even this retrospective review in our centre did not conclude that the CME and CVL technique is better but it is not inferior to the conventional technique. Furthermore, the perioperative morbidity is the same in both groups. The main advantage of CME and CVL is that it allows for more precise and extensive removal of the affected area of the colon. This minimises the risk of recurrence and metastasis, thus increasing the chances of a successful outcome. CME and CVL surgery also reduces the risk of postoperative complications such as intra-abdominal bleeding, infection and leakage.[2,4-7]

CME and CVL surgery also allows for the removal of the entire mesocolon (the connective tissue between the large and small intestine) and the main blood vessels leading to the organ.[2,4-22] This helps to reduce the risk of damage to surrounding structures and organs, which can be a major complication in conventional surgery. Yoon et al established that CME and CVL surgery is less invasive than conventional surgery and is associated with a faster recovery time.[7] The process of CME requires only a small incision, which allows for quicker healing and fewer postoperative complications.

We believe there are several limitations to our study. First of all, this is a retrospective study and is subjected to biases associated with this study design. Being a retrospective study, it does not reach the evidence level of a randomised clinical trial.[23] Secondly, this study is limited to only one single centre, which might not be representative of the whole population.

CONCLUSIONS

The CME and CVL surgery is a better approach than conventional surgery in colon surgery in a tertiary centre due to their increased accuracy and safety, reduced risk of postoperative complications, and faster recovery time. The study results indicate that there is no significant difference in survival duration between the two approaches, but CME and CVL surgery is still considered a better option due to the aforementioned advantages.

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High fibre and fluid intake increase the success of hypospadias surgery

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ABSTRACT

Introduction: Hypospadias is a congenital malformation of the urethral meatus in the ventral penis that requires surgery. Fibre and fluid intake can accelerate the healing process, act as an anti-inflammatory and support the success of surgery. Based on hypospadias objective scoring evaluation (HOSE) scoring, this study aims to determine whether a high-fibre diet and adequate fluid intake affect the outcome of hypospadias surgery.

Materials and Methods: This analytic observational study used a case-control study design on 104 post-operative hypospadias patients at Ulin and Siaga Hospital Banjarmasin from 2018 to 2023 with quota sampling. Data were collected using personal data forms with hypospadias objective scoring evaluation (HOSE) and semi-quantitative-food frequency questionnaire (SQ-FFQ), which were analysed using a multinomial logistic regression test.

Results: Patients with less-fibre-intake had a 99.10% lower chance of having an excellent surgical outcome than patients with moderate-fibre-intake (Adjusted Odds Ratio, Adj. OR: 0.009, 95% Confidence Intervals; 95%CI: 0.000, 0.249), and it was statistically significant. The study did not find any association between fluid intake and surgical outcome, this could be due to the fact that most of the patient had good fluid intake.

Conclusion: The study found that high fibre intake increases the success of hypospadia surgery.

KEYWORDS:
Hypospadias, fibre intake, fluid intake, HOSE, SQ-FFQ

INTRODUCTION

Hypospadias is a congenital malformation and tends to increase. The urethral meatus in the ventral penis is due to incomplete closure.[1] The world incidence is 1:250-300 births, and there is no exact data in Indonesia,[2,3] including Banjarmasin. The tabularised incised plate (TIP) is the most common technique for treating distal type.[4,5] Post-operative complications remain common, although surgical techniques continue evolving.[6,7] This is associated with technical factors, severity, patient condition, scarring, post-operative follow-up and infection.[8]

Nutrition and hydration support the immune system and reduce pressure during bowel movements, which is suspected to play a role in healing.[9,10]

After hypospadias surgery, it was evaluated using the functional hypospadias objective scoring evaluation (HOSE) questionnaire.[11] HOSE objectively evaluates meatus location, shape, urine flow, erection and fistula.[12] Based on the HOSE scoring, there were limited studies about the effect of a high-fibre diet and good fluid intake on hypospadias surgery.

MATERIALS AND METHODS

Study Design and Participants

The study was an analytic observational case-control study design on patients undergoing hypospadias surgery.

Setting

The study population was aged between 0 and 18 years and undergoing hypospadias surgery at Ulin and Siaga Hospital Banjarmasin from 2018 to 2023.

Study Participants

This study used non-probability sampling techniques (quota sampling) that met the inclusion criteria: post-operative patients with hypospadias for at least six months from Ulin and Siaga Hospital Banjarmasin seen in 2018-2023 and have agreed to participate. Exclusion criteria include patients with incomplete medical records. This study involved two surgeons. A paediatric surgeon was the operator, and another surgeon was the advisor. The operator determines the type of operation. For the distal types, there was 1-stage, and for the proximal, there were two or multiple stages. Generally, the first and re-operation uses the tabularised incised plate (TIP) technique. Another technique was Mathieu and transverse preputial island flap (TPIF). Each category needs 30 samples and the minimum sample is 90 people based on the theory of Gay, LR and Diehl, PL.[13]

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Table I: Bivariate analyses for demographic data and baseline characteristic of the patients.

Characteristics	Surgical outcome of hypospadias			p value
	Good (n=41)	Adequate (n=33)	Poor (n=30)	
Operative age, years (mean ± sd)	3.49±2.56	5.88±2.37	9.63±2.14	0.001[a*]
• <4 years, n (%)	26 (63.40)	7 (21.20)	0 (0.00)	0.001[b*]
• ≥4 years, n (%)	15 (36.60)	26 (78.80)	30 (100.00)	
Interview age, years (mean ± sd)	5.59±2.31	8.58±2.30	12.20±2.82	0.001[a*]
Domicile, n (%)				
• South Kalimantan	34 (82.90)	26 (78.80)	22 (73.30)	0.620[b]
• Outside of South Kalimantan (Central Kalimantan and East Kalimantan)	7 (17.10)	7 (21.20)	8 (26.70)	
Type of hypospadias, n (%)				
• Glanular	23 (56.10)	6 (18.20)	7 (23.30)	0.001[b*]
• Distal	14 (34.10)	11 (33.30)	12 (40.00)	
• Proximal	4 (9.80)	16 (48.50)	11 (36.70)	
Surgical technique, n (%)				
• TIP	37 (90.20)	25 (75.80)	21 (70.00)	0.086[b]
• Non-TIP (Mathieu and TPIF)	4 (9.80)	8 (24.20)	9 (30.00)	
Surgical stage, n (%)				
• 1 stage	34 (82.90)	15 (45.50)	12 (40.00)	0.001[b*]
• 2 stages	7 (17.10)	18 (54.50)	18 (60.00)	
Location of surgery, n (%)				
• Ulin Hospital Banjarmasin	12 (29.30)	7 (21.20)	4 (13.30)	0.276[b]
• Siaga Hospital Banjarmasin	29 (70.70)	26 (78.80)	26 (86.70)	
Time of surgery, n (%)				
• 2022-2023	20 (48.80)	12 (36.40)	11 (36.70)	0.475[b]
• 2020-2021	16 (39.00)	12 (36.40)	11 (36.70)	
• 2018-2019	5 (12.20)	9 (27.30)	8 (26.70)	
Other congenital abnormalities, n (%)				
• Present (fistula, cryptorchidism, webbed & buried penis, and hydrocele)	3 (7.30)	5 (15.20)	4 (13.30)	0.540[b]
• Absent	38 (92.70)	28 (84.80)	26 (86.70)	
Complication based on type of hypospadias, n (%)				
• Fistula	2 (100.00)	2 (100.00)	2 (100.00)	0.287[b]
Glandular	1 (50.00)	0 (0.00)	1 (50.00)	
Distal	1 (50.00)	0 (0.00)	0 (0.00)	
Proximal	0 (0.00)	2 (100.00)	1 (50.00)	
• Webbed penis	1 (100.00)	0 (0.00)	1 (100.00)	0.157[b]
Glandular	1 (100.00)	0 (0.00)	0 (0.00)	
Distal	0 (0.00)	0 (0.00)	1 (100.00)	
Proximal	0 (0.00)	0 (0.00)	0 (0.00)	
• Buried penis	0 (0.00)	0 (0.00)	1 (100.00)	NA
Glandular	0 (0.00)	0 (0.00)	0 (0.00)	
Distal	0 (0.00)	0 (0.00)	1 (100.00)	
Proximal	0 (0.00)	0 (0.00)	0 (0.00)	
• Others	0(0.00)	3(100.00)	0(0.00)	NA
Glandular	0(0.00)	0(0.00)	0(0.00)	
Distal	0(0.00)	1(33.33)	0(0.00)	
Proximal	0(0.00)	2(66.67)	0(0.00)	
• Absent	38 (100.00)	28 (100.00)	26 (100.00)	0.007[b*]
Glandular	21 (55.30)	6 (21.40)	6 (21.40)	
Distal	13 (34.20)	10 (35.70)	10 (35.70)	
Proximal	4 (10.50)	12 (42.90)	10 (38.50)	

TIP = Tabularised incised plate; TPIF = Transverse Preputial Island Flap; a = Kruskal-Wallis test; b = chi-square test; n = number; SD = standard deviation; NA = not applicable; *Statistically significant (p<0.05).

Participants Data

This data obtained from medical records included name of patient, place and date of birth, place and date of surgery, age at surgery, age at interview, house address, type of hypospadias, surgical technique employed, stage of surgery, other congenital abnormalities and telephone number as guide. The interviews were based on the HOSE questionnaire to assess the outcome of hypospadias surgery at least six months post-operatively and the semi quantitative-food frequency questionnaire (SQ-FFQ) modified by the Indonesian Food Consumption Table, FatSecret and nutritional value, to identify the patient eating and drinking history.

The participants diet history was converted using the NutriSurvey application software to calculate the daily fibre and fluid intake. The calculation was based on the table of adequate fibre and fluid intake figures by the Ministry of Health of the Republic of Indonesia. The data is interpreted in percentages and categorical data and analysed to determine the effect of a high-fibre diet and adequate-fluid-intake on the hypospadias surgery. The fibre intake was categorised as

Table II: Odd ratio for surgical outcome of Hypospadias among fibre intake.

Fiber intake	Poor (n=30)	Adequate (n=33)	Good (n=41)	Surgical outcome of hypospadias							
				Adequate				Good			
				Crude OR (95%CI)	p-value	Adj. OR (95%CI)¥	p-value	Crude OR (95%CI)	p-value	Adj. OR (95%CI)¥	p-value
Good, n (%)	0(0.00)	0(0.00)	0(0.00)	NA	NA	NA	NA	NA	NA	NA	NA
Moderate, n (%)	2(6.70)	11(33.30)	33(80.50)	1		1		1		1	
Less, n (%)	7(23.30)	17(51.50)	8(19.50)	0.442 (0.077-2.528)	0.359	0.101 (0.006-1.753)	0.115	0.069 (0.012-0.399)	0.003*	0.009 (0.000-0.249)	0.005*
Deficit, n (%)	21(70.00)	5(15.20)	0(0.00)	0.043 (0.007-0.261)*	0.001*	NA	NA	NA	NA	NA	NA

n = number; OR = odds ratio; Adj. = Adjusted; CI = confidence interval; NA = not applicable; ¥Adjusted on age at surgery, type of Hypospadias, surgical technique, surgical stage, other congenital abnormalities and fluid intake; *Statistically significant (p<0,05).

Table III: Odd ratio for surgical outcome of Hypospadias among fluid intake.

Fiber intake	Poor (n=30)	Adequate (n=33)	Good (n=41)	Surgical outcome of hypospadias							
				Good				Adequate			
				Crude OR (95%CI)	p-value	Adj. OR (95%CI)¥	p-value	Crude OR (95%CI)	p-value	Adj. OR (95%CI)¥	p-value
Good, n (%)	24 (80.00)	32 (97.00)	41 (100.00)	1		1		1		1	
Less, n (%)	6 (20.00)	1 (3.00)	0 (0.00)	0.125 (0.014-1.108)*	0.062	0.127 (0.001-11.938)	0.373	NA	NA	NA	NA

n = number; OR = odds ratio; Adj. = Adjusted; CI = confidence interval; NA = not applicable; ¥Adjusted on age at surgery, type of Hypospadias, surgical technique, surgical stage, other congenital abnormalities and fluid intake; *Statistically significant (p<0,05).

Good, Moderate, Less and Deficit. To increase the accuracy and reduce bias, the fibre and fluid intake chart determinations were carried out by medical students and supervised by nutritionists. The tool for measuring fibre and fluid intake is the most accurate tool that nutrition or food experts use to analyse consumption survey results quickly and can adjust to age and gender. The participants demographic data and essential characteristics were based on the medical student's HOSE scoring with good, adequate and poor categories.

Ethical Considerations
The study was approved the Ethics Committee of the Faculty of Medicine and Health Sciences, Lambung Mangkurat University (No. 265/KEPK-FK-ULM/EC/IX/2023), Research Ethics Committee (No. 217/X-Reg-Riset/RSUDU/23), and the Research Permit Hospital (No. 205/S1.Ked/Litbang/RSUDU/X/2023).

Data Analysis
The statistical analysis was perform using the International Business Machines Statistical Program for Social Science (IBM SPSS) version 29 for macOS. One-way ANOVA test was used for numerical and chi-square test for categorical data were. To assess the crude odds ratio (OR), Aajusted (Adj.) OR and 95% confidence interval (95% CI), a multinomial logistic regression test was conducted. All analyses used a 95%CI (α=0.05) and were statistically significant, if the p-value <0.05 or the 95% CI did not include 1.00. To minimise bias, the surgeon(s) were not involved in the data analyses.

RESULTS

Characteristics
There were 104 patients who met the inclusion and exclusion criteria. Seventy-one patients (68.30%) were interviewed online, and 33 (31.80%) were interviewed at their home or at Siaga Hospital Banjarmasin. All study respondents agreed to participate in the study. Forty-one (39.40%) had good surgical outcome (HOSE score: 14-16), 33 (31.70%) had adequate (HOSE score: 12-13) and 30 (28.80%) had poor (HOSE score: 10-11) outcome.

The most common post-operative complication was a fistula where corrective surgery was required and there were no patient with meatal stenosis. Patient who had excellent result was in glandular and distal types. The operations on the proximal type need to be evaluated to provide better results in the future. (Table I).

Comparing Surgical Outcome based on characteristics of patients
The demographic data and the essential characteristics of the patients were compared with surgical outcome (Table I). Younger patient has better outcome (Good: 3.49±2.56 years old vs. Adequate: 5.88±2.37 years old vs. Poor: 9.63±2.14 years old). Patients in the <4 years age group had a better operative outcome as compared to those ≥4 years.

There were no statistically difference in the surgical outcome based on where they lived. There was a statistically difference in the surgical outcome based on the type of hypospadias. The TIP was the most common technique employed. Based on the stage of surgery, patients with stage 1 disease had a statistically better outcome compared to stage 2 disease. There were no difference in the surgical outcome based on where the surgery was completed, the time of the surgery and the presence of other congenital abnormalities.

Comparing fibre intake and surgical outcome
Table II showed univariate and multivariate analysis to assess the relationship between the effect of a high-fibre diet and hypospadias surgery outcomes. There was no patient in the category of good fibre intake. More patient with good surgical outcome had moderate . (33, 80.50%) to less (8, 19.50%) fibre intake. Most of the patient with poor outcome had deficit (21, 70.00%) fibre intake.

Post-operative patients with less-fibre intake had a lower odds of a good outcome compared to those with moderate-fibre intake (Adj. OR: 0.009, 95%CI: 0.000, 0.249).. The data analysis showed that hypospadias surgery tends to have good surgical outcomes with a higher fibre intake.

Comparing the effect of Fluid Intake and surgical outcome
The univariate and multivariate analysis results to investigate the effects of adequate fluid intakeand hypospadias surgery outcomes are presented in Table III. Most of the patient had good fluid with 100% of those with good surgical outcome, and 97% and 80% of those in the moderate and poor surgical outcome group respectivelly. There were no statistically significant between fluid intake and surgical outcomes.

DISCUSSION

Hypospadias is one of the most common congenital malformations that is increasing in prevalence.9 It is a mild form of 46XY abnormality in the development of masculine genital organs and is often associated with impaired primary sex formation or sexual activity in adulthood.[14,15] Hypospadias can be a combination of any or all of three anatomical anomalies of the penis, which are: (1) urethral meatus in the ventral penis and more proximal than average (tip of glans penis), (2) penile curvature (chordee) and (3) ventral preputium deficiency.[16-18]

Nutrition and hydration are essential for post-operative hypospadias. Adequate fibre can support the immune system and reduce pressure during defecation.[9,10] Children who had hypospadias surgery are at higher risk of UTI; hydration with adequate-fluid intake can help to reduce the risk of infection.[19,20] Excess pro-inflammatory cytokines are released, resulting in a disturbance in wound healing.[21] Fibre and fluids are essential in this process and can accelerate the healing wound process as an anti-inflammatory to reduce the risk of post-operative complications.[9,22,23]

Patient's Characteristics
Children aged 6-18 months are recommended for surgery for psychological reasons, toilet training, consideration of penis size dimensions and post-operative complications. Operations over two years have more significant complications than those under two years. Poor compliance

with prescribed medication, increased activity and genital/stent awareness and sub-optimal stent anchorage or application of dressings are the main complication factors.[24] The first-year penis growth determines the success of the operation, and delaying surgery will be detrimental.16 More accessible care and less psychological disturbance are the advantages when operated before two years.[25]

The glandular type has the mostly good-surgical results, at 56.1%. The distal type is more complex and lengthier in surgical procedures. The meatal position is not the only consideration in reconstruction. The distal hypospadias is challenging due to small glans, poor urethral plate, proximal spongiosis and ventral curvature.[5] Around 11.5% of patients with minor congenital abnormalities did not significantly affect the surgery outcome. Understandably, minor congenital abnormalities have little influence on wound healing.

Effect of High-Fibre Diet on the Outcomes of Hypospadias Surgery
This study showed that good post-operative fibre and fluid intake increase surgery success for hypospadias. Good fibre consumption can provide good surgery outcomes. Patients with low fibre intake had a lower odds a good surgical outcome as compared to those with moderate-fibre-intake.

Constipation due to a low-fibre diet and the urinary catheter instillation stimulate straining and can cause mechanical stretching of the wound.[26] Wound healing is a unique process, including in hypospadias. Mechanical stretching improves wound healing to a certain degree, but excessive mechanical stretching can harm wound healing.[27] Usual wound stretch affects the wound healing pathway.[28] Fibre diet and stool softener are effective for treating constipation.[26]

This study's results align with Novikasari and Sanjaya's study, which states that a specific nutritional diet is vital to the success and improvement of healing. Tissue formation will be optimal if dietary requirements such as fibre are fulfilled. Nutritional deficiency can inhibit recovery, increasing the risk of open wounds and infection.[29]

Although it was not statistically significantly different, the results of this study support Almatsier's theory, which states that there is a relationship between nutrition, fluids, acceleration of wound healing and the immune system.[29]

Effect of Fluid Intake on the Outcomes of Hypospadias Surgery
Although not statistically significant in the analysis of the fluid effect on surgical outcomes, there is a relationship between good fluid consumption and the success of hypospadias surgery. Patients with less fluid intake also had an 87.3% lower chance of having an adequate surgical outcome than patients with good fluid intake.

The study results also support the Kayilioglu et al. study, in which adequate post-operative fluid intake is vital in providing adequate tissue perfusion, stabilising hemodynamics, and reducing morbidity.[30] Other studies state that fluids play a role in launching urine production and preventing tissue dehydration.[31,32] The more fibre and fluid intake, the more successful hypospadia surgery.

STRENGTH AND LIMITATIONS

As far as the researchers know, this is the first study to analyse the effect of a high-fibre diet and fluid intake on the results after hypospadias surgery. This study has considered (adjusted) potential confounders, such as age of surgery, type of hypospadias, surgical technique, stage of surgery and other congenital abnormalities.

The study limitations are that the sample size was not large enough,[33,34] and did not pay attention to confounding factors, including body weight and other nutritionally independent variables. Non-randomisation, absence of blinding, and interviewer/data analyser bias might also be issues in this study. The last bias was minimal because another data analyser had validated the statistical results. Prospective future research with a larger sample involving detailed dietary factors regarding protein, vitamins, zinc, and soluble or insoluble fibres, consume stool softener, randomised control trial and blinding interviewer and analyser will be done.

CONCLUSION

In conclusion, our findings demonstrated that fibre intake is an important component in hypospadias surgical outcome. Patients with less fibre intake showed a lower odds of having a good surgical outcome as compared to those with moderate fibre intake. The study did not find any significant statistic correlation between fluid intake and surgical outcome, this could be due to the fact that most of the patient had good fluid intake. High fibre and fluid intake increase the success of hypospadias surgery.

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Adverse neonatal outcome associated with maternal tuberculosis in a public tertiary centre: a retrospective cohort study

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ABSTRACT

Introduction: The aim of this study was to evaluate a group of infants born to women with tuberculosis (TB) during pregnancy to determine the neonatal morbidities and its outcomes associated with tuberculosis in pregnancy.

Materials and Methods: Data from January 2007 to December 2021 was collected for analysis as part of a retrospective cohort study. This study was conducted in a tertiary public hospital in Malaysia, Hospital Sultan Idris Shah (HSIS). Cases were identified from the hospital's bacille Calmette-Guerin (BCG) vaccination notification forms and merged with records from the neonatal intensive care unit's census. Controls were infants born to mothers unaffected by TB within the same hospital and year as the index case (1:4 ratio). Descriptive statistics and logistic regression were used to analyse the data. The main outcome measures were the risk of congenital tuberculosis, premature birth, low birth weight, small for gestational age and low APGAR score.

Results: Infants born to mothers with TB exhibited a two-fold increased risk of low birth weight (Odds Ratio, OR: 2.51; 95% Confidence Interval, 95%CI: 1.31, 4.81), with an even higher risk (OR: 3.29; 95%CI: 1.637, 6.612) if active TB was diagnosed during the index pregnancy. These infants also had an elevated risk of being small for gestational age compared to infants born to healthy mothers (OR: 2.48; 95%CI:1.15, 5.39). Furthermore, adverse outcomes were also more frequently detected among infants of mothers with pulmonary TB compared to those with extra-pulmonary TB. Infants born to mothers with PTB were more likely to be born with low birth weight (OR: 1.60; 95%CI: 1.095, 2.339). No cases of congenital TB were reported throughout the entire study period.

KEYWORDS:
Low birth weight, maternal, neonatal, respiratory failure, tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the foremost infectious diseases worldwide, persisting as a significant health concern in many countries. According to the World Health Organization (WHO), the global estimates place the number of individuals infected with TB were at 10 million, with the majority (45%) originating from Southeast Asian countries.[1] As per the latest statistics, Malaysia is categorised as a nation grappling with an intermediate TB burden.[1] In 2022, Malaysia recorded an estimated TB incidence rate of 113 per 100, 000 population, with female aged 15 and above constituting approximately 33% of those affected.[2]

The impact of TB on pregnancy outcomes is well-documented.[3] A comprehensive analysis, involving 3384 pregnancies with TB, revealed that pregnant women with active TB were found to have increased odds of maternal morbidity, anaemia in pregnancy, caesarean birth and preterm birth compared to their healthy counterparts.[3] In addition TB is also recognised as one of the primary causes of non-obstetric maternal mortality, particularly in countries with a high prevalence of human immunodeficiency virus (HIV) infection.[4-6] Conversely, there is inconsistency in reports regarding the effect of TB on the unborn foetus. Some series have documented complications such as prematurity, low birth weight and increased neonatal mortality.[7-11] However; other studies have indicated no discernible difference in foetal outcomes between mothers with TB during pregnancy and unaffected mothers.[12-14]

Despite our status as an endemic country, there is still a lack of published data on tuberculosis infection among pregnant women and its impact on the unborn baby. This study was designed to assess the neonatal outcome of infants born to women with tuberculosis during pregnancy in our country.

MATERIALS AND METHODS

We conducted a retrospective analysis of the medical records for 30 consecutive infants born to mothers whose pregnancies were complicated with TB infection. These births occurred at a tertiary-level public hospital between January 2007 and December 2021. Cases were identified from the departmental records where infants of TB mothers were routinely admitted for evaluation and management. Inclusion criteria comprised of infants born to all mothers who either conceived while undergoing anti-tuberculosis therapy or were diagnosed with TB during pregnancy or the postpartum period. The diagnosis of TB was confirmed through clinical

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Table I: Neonatal outcome associated with TB infection in pregnancy compared to control (n = 150).

Neonatal outcome	Mother with TB (n=30) n (%)	Mother without TB (n=120) n (%)	p-value	OR (95%CI)
Birth weight (kg) median (IQR)	3.06 (0.8)	3.024 (0.5)	0.581[c]	
Prematurity (<37 weeks)				
Yes	5 (16.7)	12 (10.0)	0.336[a]	
No	25 (83.3)	108 (90.0)		
Birth weight				
low	8 (26.7)	11 (9.2)	0.026[a]	2.51 (1.31 – 4.81)
normal	22 (73.3)	109 (90.8)		
Small for gestational age (SGA)				
Yes	6 (20.0)	11 (9.2)	0.110[a]	
No	24 (80.0)	109 (90.8)		
APGAR score <7 at 1 minute of life				
Yes	1 (3.3)	6 (5.0)	1.000[b]	
No	29 (96.7)	114 (95.0)		

a = Pearson Chi-square, b = Fisher exact test, c= Mann Whitney

Table II: Neonatal outcome associated with active TB infection during pregnancy compared to control (n=144).

Neonatal outcome	Mother with active TB (n=24) n (%)	Mother without TB (n=120) n (%)	p-value	OR (95% CI)
Birth weight (kg) median (IQR)	3.100 (1.0)	3.08 (0.5)	0.612[c]	
Prematurity (<37 weeks)				
Yes	5 (20.8)	12(10.0)	0.163[b]	
No	19 (79.2)	108 (90.0)		
Birth weight				
Low	8 (33.3)	11 (9.2)	0.004[a]	3.29 (1.637-6.612)
Normal	16 (66.7)	109 (90.8)		
Small for gestational age (SGA)				
Yes	6 (25.0)	11 (9.2)	0.040[a]	2.49 (1.15-5.39)
No	18 (75.0)	109 (90.8)		
APGAR score <7 at 1 minute of life				
Yes	1 (4.2)	6 (5.0)	1.000[b]	
No	23 (95.8)	114 (95.0)		

a = Pearson Chi-squared , b = Fisher exact test, c = Mann Whitney

Table III: Neonatal outcome associated with PTB compared to EPTB infection in pregnancy (n = 24).

Neonatal outcome	Mother with PTB (n=18) n (%)	Mother EPTB (n=6) n (%)	p-value	OR (95% CI)
Birth weight (kg) median (IQR)	2.765 (1.0)	3.485 (0.6)	0.026b	
Prematurity (< 37 weeks)				
Yes	5 (27.8)	0 (0.0)	0.147[a]	
No	13 (72.2)	6 (100.0)		
Birth weight				
Low	8 (44.4)	0 (0.0)	0.046[a]	1.60 (1.095-2.339)
Normal	10 (55.6)	6 (100.0)		
Small for gestational age (SGA)				
Yes	6 (33.3)	0 (0.0)	0.102[a]	
No	12 (66.7)	6 (100.0)		
APGAR score< 7 at 1 minute of life				
Yes	1 (5.6)	0 (0.0)	0.550[a]	
No	17 (94.4)	6 (100.0)		

a = Fisher exact test, b = Mann Whitney

manifestations of active infection, along with supporting evidence from acid-fast-bacilli (AFB) stains, Mycobacterium tuberculosis culture or histological studies. Cases with missing or irretrievable medical records were excluded from analysis.

We employed a purposive sampling strategy to select control, each infant born to a mother with a TB case was paired with four infants (1:4 ratio) born to mothers unaffected by TB within the same hospital and year as the index case. Subsequently, we randomly selected samples from the control group, and matched them to the cases based on maternal age and maternal morbidities, which included diabetes mellitus and/or gestational diabetes, as well as pre-existing hypertension and/or pregnancy-induced hypertension.

The medical records of both cases and controls were retrieved from the hospital's electronic medical records system. Subsequently data on primary neonatal outcomes or dependent variables including prematurity (defined as birth occurring before 37 completed weeks), birth weight, low birth weight (defined as birth weight less than 2,500 grams), small for gestational age (SGA) (defined as a birth weight below the 10th centile for age and gender), low APGAR score at 1 minute of life (defined as APGAR score less than 7 at 1 minute of life) and congenital TB were carefully identified, extracted and recorded into a standardised proforma. Additionally, maternal TB status, an independent variable, was also noted and recorded for further analysis. Congenital TB was defined as an infant presenting with a proven tuberculosis lesion associated with one of the following conditions: the lesion occurring in the first week of life, primary hepatic complex, maternal genital tract or placental tuberculosis or exclusion of postnatal transmission through a comprehensive investigation of contacts.[15]

The analysis of all data was carried out using IBM Statistical Package for the Social Sciences software, version 29.0 (SPSS Inc., Chicago, USA). Cohort comparability was assessed using the test of proportion, while descriptive analysis summarises the study population's demographics, with mean or median and standard deviation or interquartile range for continuous data, frequencies and percentages for categorical variables. We then compared the categorical variables between cases and controls using Pearson chi-squared test or Fisher exact test. Non-parametric test which is the Mann-Whitney test was performed to compare the birth weight between the two groups. Then multinomial logistic regression analysis was conducted with a power of 80% and a confidence level of 95% (95%CI). A p-value of <0.05 was considered statistically significant. Then, we computed the odd ratio and determined a 95% confidence interval to identify potential associations. Ethical approval was granted by the National Institute for Health (NIH) Malaysia (ref: NMRR ID-23-02386-ZNR).

RESULTS

During the study period, a total of 30 infants born to mothers diagnosed with TB infection were included. These mothers age ranged from 20-38 years, with a median age of 29 years. Out of the 30 mothers diagnosed with TB, 21 (70.0%) had pulmonary TB, while the remaining nine (30.0%) suffered from extrapulmonary infection: seven had lymph nodes involvement, one had spinal TB and one had pleural TB. Among all cases of TB infection, six mothers (20%) conceived while undergoing anti-tuberculous therapy, while in 12 mothers (40%), treatment was initiated during the early stages of pregnancy. Anti-TB treatment was commenced during the second and third trimester in seven cases (23.3%) and five cases (16.7%) respectively.

A total of 120 healthy mothers constituted the control group, and they were comparable to the group of mothers with TB infection in terms of age, parity, nationality, ethnicity and pregnancy-related complications.

Neonatal outcome, including prematurity and small for gestational age, were observed as higher rates among infants born to mothers with TB compared to those born to healthy mothers (16.7 vs. 10.0% and 20.0 vs. 9.2% respectively) (Table I). However, bivariate analysis did not reveal any statistically significant difference (p>0.05). Infants born to mothers with TB exhibited a two-fold increased risk of low birth weight (OR 2.51; 95%CI: 1.31 – 4.81), with an even greater risk observed if active TB was diagnosed during pregnancy (OR 3.29; 95%CI: 1.637 – -6.612) (Table II). These infants also had an elevated risk of being small for gestational age compared to infants born to healthy mothers (OR 2.49; 95%CI: 1.15 – 5.39). Neonatal outcomes were more frequently observed among infants born to mothers with pulmonary TB compared to those with extra-pulmonary TB (Table III). While there were no significant statistical differences were found in the rates of premature birth, SGA and low APGAR score at 1 minute of life between the two groups, we found that infants born to mothers with PTB were more likely to be born with low birth weight (OR 1.60; 95% CI 1.095 – 2.339). Notably, no cases of congenital TB or neonatal mortality were reported throughout the study period.

DISCUSSION

As mentioned by several studies, maternal infection with Mycobacterium tuberculosis during pregnancy may pose a risk for foetal complications.[7,8,11] In a study by Narayan Jana and colleagues from Northern India, infants born to mothers with pulmonary TB exhibited a two-fold increase in the risk of foetal distress (RR: 2.4; 95%CI: 1.2 – -4.7), low birth weight (RR: 2.1; 95%CI: 1.4 – 3.1), SGA (RR: 2.6; 95%CI 1.4 – 4.6), prematurity (RR: 2.1; 95%CI: 1.2 – 3.4) and a six-fold higher risk of perinatal mortality (RR: 6.4; 95%CI: 2.2 – 18.4) compared to healthy controls.[7] Similar outcome were reported to be associated with extrapulmonary tuberculosis during pregnancy (except TB lymphadenitis).[8] This finding is consistent with observations reported by Chopra et al.,.[11] Our study aims to emphasise the effects of TB infection on newborns by comparing two cohorts from the study hospital.

The results from the current study revealed a significant relationship between TB infection during pregnancy and both low birth weight and being small for gestational age. The risk of being born with low birth weight or being small for gestational age was three to four times higher if active TB was diagnosed during pregnancy. This risk was even more pronounced when the diagnosis of infection was delayed, leading to a delay in the initiation of the anti-TB regimen.

Our findings align with the results obtained by other researchers who have documented similar neonatal outcomes.[12,13,16] Lin et al., discovered significantly higher percentages of low birth weight and infants being small for gestational age among those born to mothers with TB infection during pregnancy, as compared to unaffected mothers.[12] In a recent population-based retrospective cohort study involving 243,682 deliveries in Israel, significantly higher rates of very low birth weight infants (birth weight <1500gm) were reported among mothers with TB compared to those born to healthy mothers (4.3 vs. 0.6%, p-value 0.03).[15] Additionally, women with latent tuberculosis showed significantly higher rates of very low birth weight infants (5.6%), compared to women with active tuberculosis during pregnancy and those without tuberculosis (0.6% and 0.0%, respectively) (p<0.001).[16] Conversely, Asuquo et al. analysed data from babies born to 24 mothers with TB in three hospitals in Birmingham, United Kingdom, in 2012, and they reported no differences in the rates of low birth weight and small for gestational age when compared to the healthy subjects.[17] Likewise, a population-based survey that included 7.8 million births in the United States did not identify any adverse neonatal outcomes among infants born to mothers with TB during pregnancy.[14] The inconsistencies in findings among these studies can be attributed to underlying differences in study design, patient selection, geographical variations, time periods and sample size. Furthermore, some investigators did not adequately control for certain confounding factors, such as common pregnancy-related complications like pregnancy-induced hypertension and gestational diabetes. The effects of TB on premature birth, low birth weight or small for gestational age could be indirectly influenced by placental insufficiency secondary to pregnancy-induced hypertension and gestational diabetes. In such cases, complication rates might be falsely high. To mitigate such issues, we matched the control subjects with the cases based on the presence of comorbidities.

Unfortunately, due to the nature of our study, our dataset did not allow for a detailed analysis of other potential confounding factors that may have adversely affected birth weight, such as socioeconomic factors, access to healthcare services and maternal nutritional status, as they were not routinely documented.

The in-utero growth of the foetus relies entirely on the functioning uteroplacental unit. TB infection or reactivation of latent TB may make pregnant women more susceptible to tuberculous bacillaemia. Consequently, the infection can disseminate to multiple organs, including the placenta and the maternal genital tract. Additionally, it can be vertically transmitted to the unborn foetus through the umbilical vein or by aspiration or ingestion of contaminated amniotic fluid. These transmissions can lead to the formation of primary complex in the liver, lung or gastrointestinal tract of the foetus.[17] In our cohort of patients, no babies were born with congenital TB and there were no reported neonatal deaths among infants born to mothers with TB. These findings contrast with previous observations from studies conducted in India, Mexico and United Kingdom,[7,19,20] where a three- to six-fold perinatal mortality rates was observed among infants born to mothers with TB compared to unaffected mothers. However, it's important to note that all the perinatal deaths in those studies were attributable to complications of prematurity and small for gestational age.

Compared to earlier studies, both our study and more recent series have reported similarly improved outcomes. This can be attributed to significant advances in the healthcare system, as well as the improved socioeconomic and nutritional status of pregnant mothers. The majority (83.3%) of our cases were diagnosed rather early, either just prior to conception or during the first two trimesters. Only five cases were diagnosed late in the third trimester, Moreover, the early administration of the anti-TB regimen was effective in preventing or, if necessary, reducing the risk of adverse neonatal outcomes. Furthermore, advancements in obstetric and neonatal care have led to a lower incidence of premature birth, better overall prognosis and reduced morbidity and mortality for babies. Although concerns have been raised about the teratogenic effects of anti-TB medication, no congenital anomaly were observed among the infants in our study. Since this was a single-centre study, the results may not directly reflect the true disease burden. It is important to mention that the presence of latent tuberculosis infection (LTBI) among mothers has not been established which might impact the accuracy of the data about the prevalence of TB in the population under study. However, it has provided valuable information to stakeholders regarding the incidence rate of active TB among the population of interest, namely pregnant women in Malaysia. Given that universal screening for TB infection is not a routine practice and is typically performed only when women present with symptoms, highlighting the neonatal outcomes is crucial. This information can serve to educate and encourage pregnant women to undergo TB testing.

CONCLUSION

In conclusion, we find that tuberculous infection in pregnancy is strongly associated with low birth weight and small for gestational age infants. This underscores the importance of early diagnosis and treatment of TB infection during pregnancy to mitigate neonatal outcome. Moreover, it emphasises the need for continued efforts to improve healthcare and socioeconomic conditions for pregnant mothers. Healthcare providers should consider screening women presenting for prenatal and peripartum care for tuberculosis.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

DECLARATIONS

This study was approved by the medical research and ethics committee, Ministry of Health Malaysia NMRR ID-23-02386-ZNR.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Identifying an appropriate gene testing tool for inherited retinal dystrophy in Indonesia, a developing country

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ABSTRACT

Introduction: Inherited retinal dystrophy (IRD) is a group of untreated genetic ocular diseases that mostly affect young people. The number of patients with IRD worldwide, including in developing countries, is growing each year. This literature review aimed to investigate the current utilised genetic screening of IRD worldwide and to propose the most feasible genetics test and diagnostic method for IRD in developing countries, especially Indonesia.

Materials and Methods: A literature search was performed in PubMed and Google Scholar databases. Papers conducting wide genome sequencing, including panel sequencing (panel-seq), microarray, whole exome sequencing (WES), whole genome sequencing (WGS) and Sanger sequencing on patients with IRD, were included. Papers were sorted into several groups to visualise the sequencing technology's detection rate. Detection rate comparison analysis was done using the meta-regress protocol in the R program. Whereas the number of novel mutations in each testing tool each year was pooled and compared in the graph.

Results: After conducting the literature study, 37 papers were sorted from 451 results. Most studies conducted a panel-seq with 16 records followed by WES with seven records. The detection rate of the WES meta-analysis was 0.66, which was slightly better than the panel-seq with 0.55. The number of novel mutation discoveries fluctuated each year with panel-seq as the most prominent finder. Cost factors and the limitation of sequencing devices make panel-seq a more appropriate tool in Indonesia.

Conclusion: The most effective selection for evaluated genetic testing was WES. Therefore, panel-seq is more suitable for first-tier genetic testing in Indonesia.

KEYWORDS:
Inherited retinal dystrophy, whole genome sequencing, diagnostic rate, novel mutations discovery, suitable genetic testing

INTRODUCTION

Inherited retinal dystrophy (IRD) is a group of untreated genetic ocular diseases that mostly affect young people.[1] Disease manifestations and genetic background of IRD are heterogeneous. So far, 281 genes have been associated with IRD (https://web.sph.uth.edu/RetNet/home.htm). The damaged retinal cells tend to compromise the patient's sight partially or completely. At the minimum, 20 IRD types were identified including retinitis pigmentosa (RP), Stargardt disease, rod-cone dystrophy (RCD) and Leber congenital amaurosis (LCA).[2-4]

The number of people around the world affected by IRD is increasing every year, and approximately one in 3,000 to 5,000 individuals are affected by IRD.[5] However, the disease prevalence in Indonesia was not available until this paper was finished. The actual estimation is challenging since the advanced diagnostic tools are not evenly distributed across all nations. Furthermore, suspected IRD patients must be diagnosed by a vitreo-retina specialist.

IRD is also known to severely decrease young people's quality of life and poses a heavy psychological and economic burden. People's awareness of getting a check-up for any IRD symptoms varied in the global population.

The clinical features of IRD vary among individuals, but the key features of each type of IRD are unique and often include retinitis pigmentosa with arteriolar attenuation, retinal pigmentary changes (hypopigmentation/hyperpigmentation of bone-spicule and pigment clumping) and waxy disc pallor. Several IRDs exhibit similar features at the late stages, such as severe retinal cell death, extensive atrophy of the retina, and irreversible visual loss.

To further clarify the diagnosis, these genetically heterogeneous retinal dystrophies, such as cone dystrophies (CD), cone-rod dystrophy (CRD), Leber congenital amaurosis, and retinitis pigmentosa, present significant challenges, since mutations can be expected in any of 8–61 genes. A powerful screening method for these genes or variants with cost-effectiveness was needed.

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Commonly used genetic testing tools globally in IRD cases include Sanger sequencing, microarray and next generation sequencing (NGS) technology. The NGS technology can be costumed into panel-based NGS (panel sequencing [panel-seq]), whole exome sequencing (WES), and whole genome sequencing (WGS). These technologies' principles were different and yielded varied diagnostic rates.

Although all sequencing instruments (Sanger and NGS) were available in Indonesia, genetic screening of IRD was uncommon in Indonesia. Genetic screening was limited to the field of research.[6,7] The genetic screening is not included in the diagnosis due to high prices and the clinical meaning. Currently, it is not feasible, and the genetic data is not used for further treatment consideration.

Ideally, patients with known genetic backgrounds can be treated more effectively than those with unknown ones. To begin a big plan for genetic therapy trials in Indonesia, the Indonesian team must begin to classify their patients.

In Indonesia, people with no or light symptoms are not likely to visit an ophthalmologist, while those suspected with severe symptoms are less motivated to be referred to the tertiary hospital after knowing that their condition is untreated. Similarly, the lack of awareness couple with IRD symptoms could produce an affected baby since the accumulation or the combination of genetic mutations might increase the risk of the disease onset or compound its severity.

This review aimed to investigate the most feasible IRD genetic screening method for a developing country such as Indonesia.

MATERIALS AND METHODS

Systematic searching for literature citations in this review was conducted in July 2022 with Boolean operators using terms 'inherited retinal dystrophy', 'inherited retinal dystrophies' and 'genome sequencing', 'whole genome sequencing', 'wide genome sequencing', 'whole exome sequencing', 'targeted sequencing', 'panel sequencing'; 'next generation sequencing' through the PubMed and Google Scholar databases. The screening procedure allowed the authors to exclude the less suitable references, i.e. systematic review, book chapters, comments and not genetic study. A flow diagram of the systematic search was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The pooled detection rate of each genetic tool was analysed using the meta-regress protocol in the R program. The novel mutation discovery of each genetic tool each year was tabulated on a graph.

RESULTS

Suitable Genetic Testing Instrument

After conducting the manuscript screening, the eligible papers were tabulated and filtered (Figure 1). First, from matched 451 papers, duplication (n=6), and not original articles i.e. reviews, book chapters, and comments (n=238) were excluded. Secondly, the original article, but not a human genetics study was excluded (n=12). Third, papers with missing data or reports not retrieved (n=12) were excluded. Lastly, the paper does not elaborate on the number of solved and unsolved cases (n=12) and shows a high deviation (n=134) not included in the meta-analysis.

In the current review, five sequencing methods performances were compared, i.e. microarray, WGS, Sanger sequencing, panel sequencing, and WES. The detection rates of those five methods were 0.35, 0.39, 0.44, 0.55 and 0.65, respectively. In this analysis, WES has the highest positive rate.

Astuti performed studies using microarray sequencing in 2016,[8] Cauwenbergh in 2017,[9] and Barandika in 2015[10] with a total of 173 samples. Among those three, Barandikaa's study which tested 76 samples, had the highest detection rate of 0.32 with a weight of 44.5%.

The Sanger method sequenced a total of 498 samples with a detection rate of 0.44. The largest detection rate in the Ramkumar's in 2017[11] with 225 samples was 0.40 with a common weight of 45.7%.

The WGS method, with a total of 324 samples from the one conducted by Biswas in 2021,[12] Carss in 2017,[13] and Numa in 2020[14] showed a random effects model of 0.39. In this review, it was found that the WGS method in Numa's study with 171 samples had the most accurate diagnostic rate of 0.26 with a random weight of 38.5%.

Of the 37 analysed studies, 16 of them used the panel sequencing method, with a total of 4,350 samples having a detection rate of 0.55. Carss in 201713 used 722 samples with a detection rate of 0.56 and a common weight of 16.7%. Seven studies using the WES method with a sample size of 1374 had a detection rate of 0.65. Whelan, in 2020[15] with a sample size of 710, had the highest detection rate of 0.70 with a random weight of 27.4%.

After conducting correlation testing, the best pooled diagnostic rate for IRD was WES (0.66) then, followed by panel sequencing (0.55). The microarray, Sanger and WGS yielded less than 0.5 diagnostic rates.

Novel Mutation Discovery

Genetic variants associated with IRD are growing as novel mutations are discovered until 2021 (Figure 4). Panel-seq was the top contributor in 2019 with 384 new variants, surpassing WES by 175.

One, 156, four and one novel mutation was discovered by using microarray in 2007, 2011, 2015 and 2020, respectively. Five, one, one, and 42 novel mutations were identified by using WGS in 2017, 2018, 2020, and 2021, respectively.

However, the number of novel mutations discovered from all devices after 2019 decreased each year.

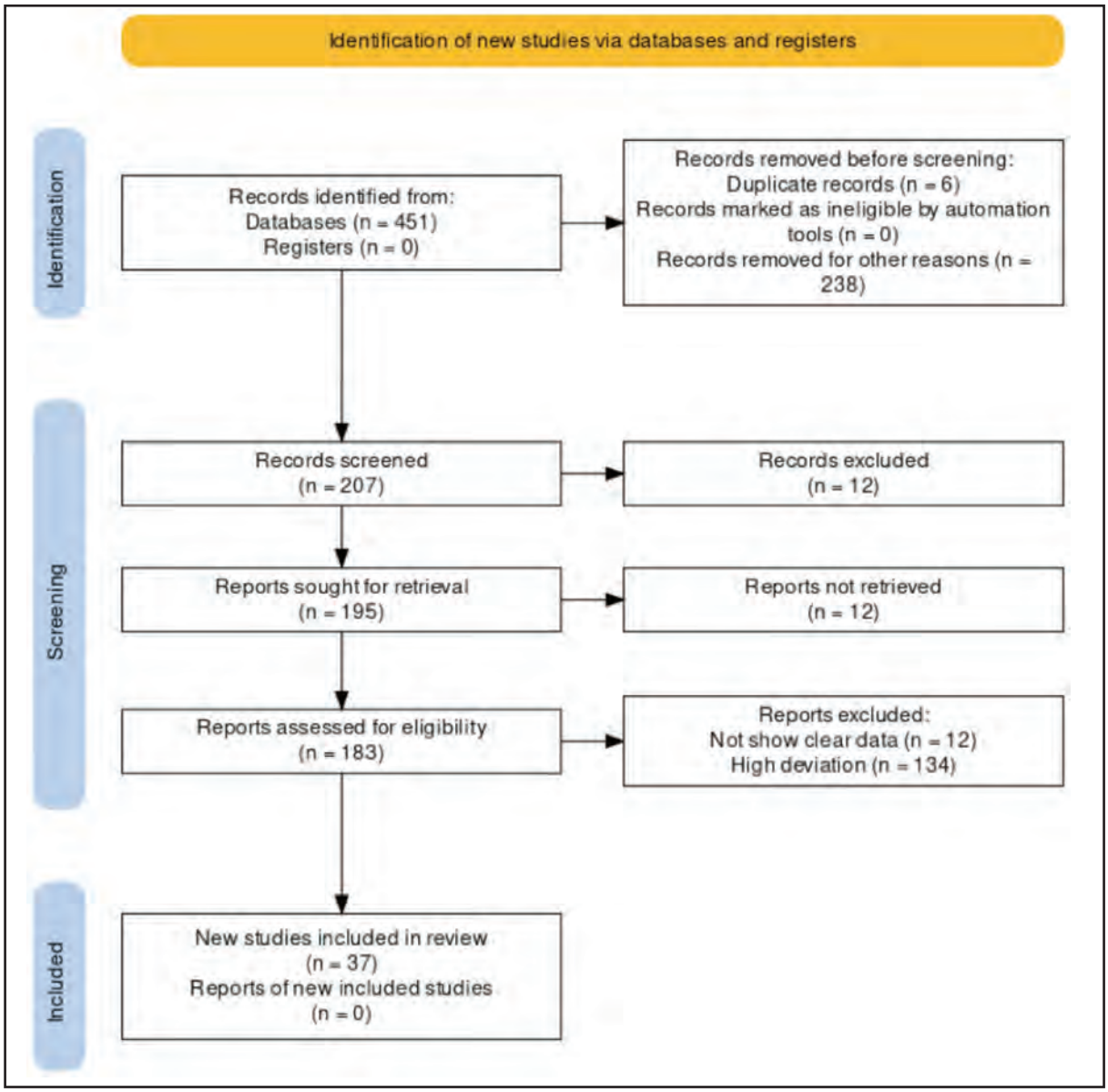

Fig. 1: The searching strategy for the review of inherited retinal dystrophy genome sequencing. After filtering the manuscripts, 37 eligible records were summarised (Table I).

DISCUSSION

The Genetic Testing Choice of IRDs

Whole exome sequencing shows a higher diagnostic rate than panel-seq in this review. The main reason was that the number of genes and variants included in each panel-seq used in each research varied. That widened the discrepancy in the diagnostic rates. On the other hand, WES included all variants and genes at the exome region by default. This created similar results to all WES research findings, which also yielded high diagnostic rate.

Although panel-seq on most research plans was placed as the first tier, this strategy did not lower the WES detection rate. The remaining unsolved IRD cases that underwent WES have yielded a good diagnostic rate. Consider using WES in research if cases remain unsolved by panel-seq.

The Sanger sequencing, as expected, had a low diagnostic rate as the narrowest type of testing. The success of Sanger sequencing depends on how specific the IRD was characterised and the loci target. Typical Sanger sequencing can read 300 nucleotides long, so the target genomic location is selected carefully. The monogenic or/and well-defined aetiology of a specific sub-type of IRD phenotype can be 100% identified by the Sanger sequencing approach.

On the other hand, a low diagnostic rate of WGS was unexpected. Theoretically, the resolving power of WGS was higher than WES, but in this review, did not yield a comparable diagnostic rate. The main concern was the last preference of using WGS in most of the research. The pooled unsolved cases from other instruments (including WES) and the complex and unclear phenotypes of IRD cases were difficult to solve even using WGS. The number of cases that

Table I: The filtered records included in the meta-analysis

No	authors	Sequencing Technology	Diagnosis Rate	Number of case
1	henderson 2007	microarray	0.44	153
2	Jin song 2011	microarray	0.79	19
3	Barandikaa 2015	microarray	0.32	76
4	Astuti 2016	microarray	0.38	40
5	Cauwenbergh 2017	microarray	0.37	57
6	Martin-Merida 2019	microarray	0.11	721
7	Neveling 2012	Panel seq	0.47	234
8	Li Zhao 2015	Panel seq	0.6	82
9	Consugar 2015	Panel seq	0.51	192
10	Zhongqi 2015	Panel seq	0.49	105
11	Patel 2016	Panel seq	0.62	292
12	Ellingford 2016	Panel seq	0.5	537
13	Carss 2017	Panel seq	0.56	722
14	Haer Wigman 2017	Panel seq	0.49	299
15	Handong dan 2019	Panel seq	0.57	76
16	Jiman 2019	Panel seq	0.52	106
17	Panfeng Wang 2019	Panel seq	0.52	568
18	Mun?oz 2020	Panel seq	0.62	172
19	Sheck 2020	Panel seq	0.59	488
20	Duzkale 2021	Panel seq	0.61	46
21	Maggi 2021	Panel seq	0.58	119
22	Ta-Ching Chen 2021	Panel seq	0.57	312
23	Sullivian 2013	Sanger seq	0.52	170
24	Astuti 2016	Sanger seq	0.41	64
25	Ramkumar 2017	Sanger seq	0.4	225
26	Collison 2019	Sanger seq	0.33	39
27	Weisschuh	wes	0.62	47
28	Riera 2017	wes	0.71	59
29	Bryant	wes	0.64	69
30	Whelan 2019	wes	0.7	710
31	Ahra Cho 2020	wes	0.57	250
32	Belal Azab 2021	wes	0.71	55
33	Yoon-Jeon Kim 2021	wes	0.6	184
34	Bujakowska 2016	wgs	0.18	28
35	Carss 2017	wgs	0.31	45
36	Numa 2020	wgs	0.26	171
37	Biswas 2021	wgs	0.56	108

underwent WGS was also lower than other instruments, making the statistics poor.

Microarray was similar to panel-seq in terms of variant customisation. Users can choose which variant and its number is included in the microarray. This makes the microarray detection rate also varied in each research. The number of studies using microarray was also limited. The reviews published during the 2000s suggested that microarray was less suitable than NGS-based methods for genotyping,16-18 which affects scientist preference.

The similarity between microarray and WES in various studies should yield a comparable diagnostic rate. However, the result of the pooled diagnostic rate of the microarray was lower than panel-seq.

The Availability and Pros-Cons of the Sequencing Platform for Highly Covered IRDs Mutation

The advanced technology has been developed to enhance the IRD genetic landscape. The number of reported loci was high, including the novel mutations. After the exhaustive use of wide genome analysis, the number of novel mutations should decrease every year.

To date, 4,798 discrete variants and 17,299 alleles were reported by Schneider in 2022.[19] Most variations are located at ABCA4 (24.8%) followed by USH2A (14.6%). Even the elusive cases of IRD were caused by a limited number of genes. So, a powerful panel-seq must be developed to substitute WES to cover all possible genetic causes of IRDs.

IRD populational genetic research in Indonesia or Southeast Asia was limited, so the current data cannot be directly interpreted for policy in Indonesia. However, the data still could suggest the most suitable genetic testing.

The prevalence of IRD and the list of common causative mutations in Indonesia remains unknown, but the total number of cases is expected to be high. The list of mutations included in the Panel can be determined only if the prevalence of causative mutations in the Indonesian population is known.

The utility of WES is no longer important if most of the associated genes were mapped. The more suitable genetic testing will be panel-seq. But at the time of developing a panel for genetic testing, the rate of new mutation discovery must be already low or not detected.

The acquired records were analysed further to pool the diagnostic rates of each technology (Figure 2).

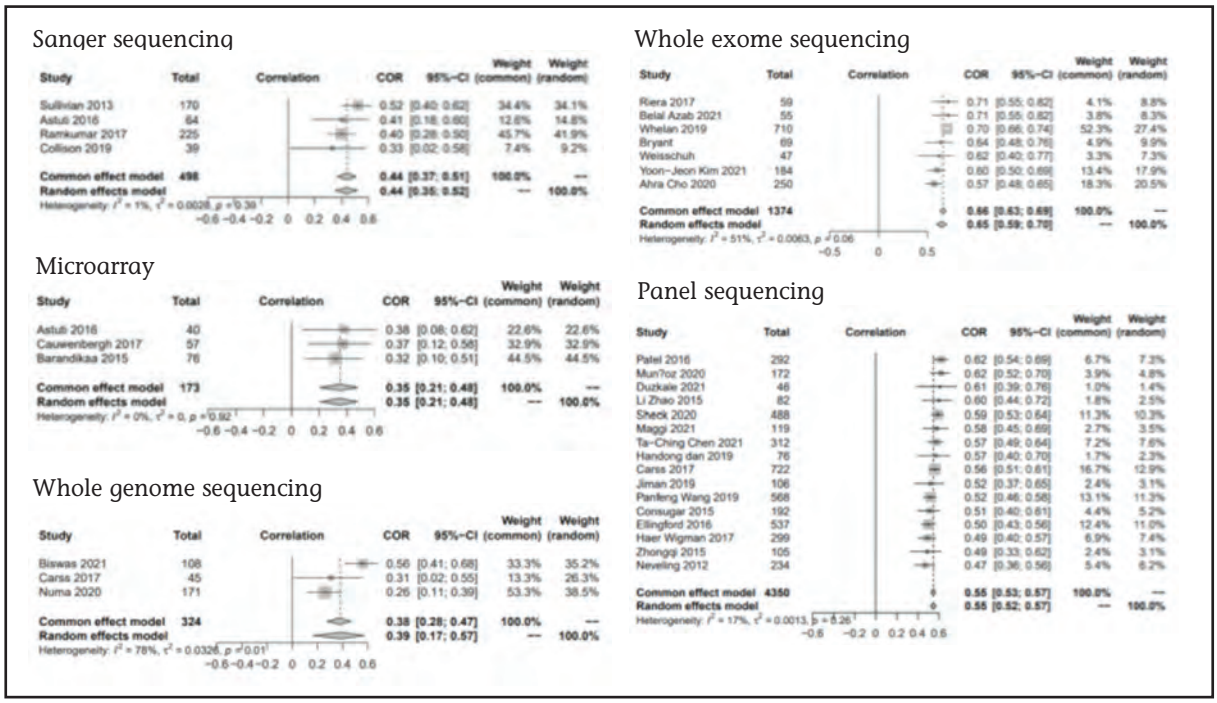

Fig. 2: Forrest Plot showing the diagnostic rate comparison of Sanger sequencing, microarray, and Next generation sequencing technologies (panel-seq, whole exome, whole genome). The whole exome yielded the highest detection rate.

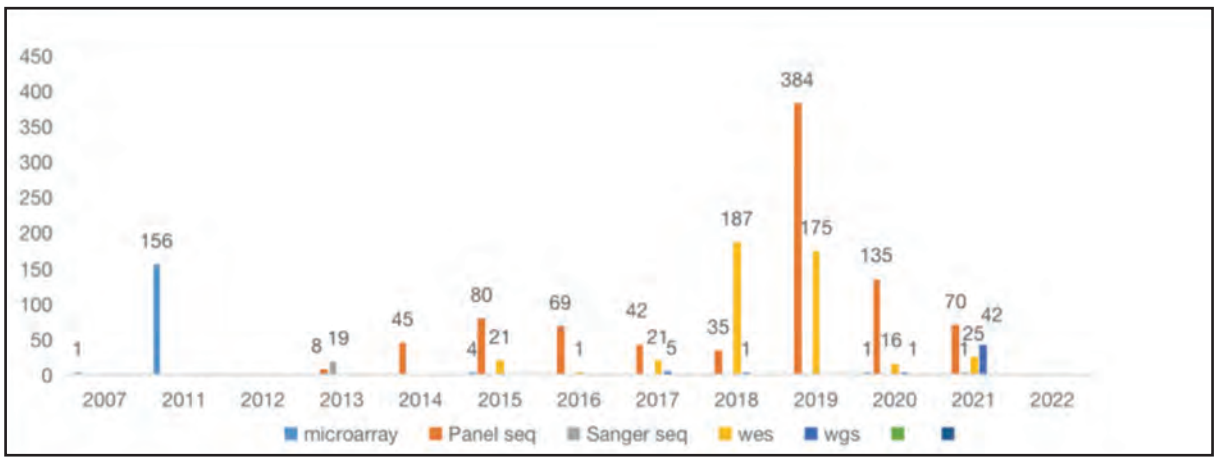

Fig. 4: The novel mutation discovery of inherited retinal dystrophy (IRD) year 2007 - 2022 by microarray, Sanger, panel, whole exome sequencing (WES), and whole genome sequencing (WGS).

The current running cost of WES was much higher than panel-seq as the routine diagnostic tool especially in Indonesia. The output data of panel-seq was also smaller than WES. It takes less effort to interpret data. So, panel-based sequencing costs will be more economical than WES. Routine diagnostics should minimise the laborious data analysis by utilising an automated pipeline.

CONCLUSIONS

Currently, the most suitable first-tier genetic testing for patients with IRD was whole exome sequencing for most IRD cases. However, for feasible genetic testing in the future, the first tier of genetic testing should be panel-seq.

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A systematic review on thalassaemia screening and birth reduction initiatives: cost to success

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ABSTRACT

Introduction: Thalassaemia has been prevalent with high morbidity and mortality rates since 1925. Although there is a lack of systematic review on the costs of prevention that has yielded reductions in thalassaemia prevalence, this review will show a widespread presence of complex but effective strategies in reducing national thalassaemia prevalence.

Materials and Methods: A systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). Designated keywords were combined with search functions and Boolean operators in databases like Scopus, Web of Science and several other search databases.

Results: The search identifed 5425 potential articles. Most countries reported a decline in thalassaemia prevalence after implementing intervention programmes for several decades. The screening methods, however, varies, and the speed of reductions depends on the type of screening approach that involves blood screening of adolescence and antenatal mothers and, in some countries, includes termination of pregnancy. In addition, the cost of these initiatives varies as it was challenging to find a common denominator. However, the endpoint concedes that the cost of screening, although substantial, would be offset by the cost of reduction of cases. In some countries, cost-effectiveness analyses have been reported to support the initiatives of thalassaemia screening and prevention in the long run.

CONCLUSION: The results showed significant variations in success rates with a significant reduction in the prevalence of Thalassaemia. Most successful are countries with comprehensive and aggressive prevention and control programmes that engaged with lab screening, counselling, and termination of pregnancy as a package.

KEYWORDS:
birth reductions, prevalence, thalassaemia, programme cost, screening methods, treatment cost

INTRODUCTION

Countries conducting thalassaemia screening and prevention programmes took several years to witness the decline in thalassemia births. The cost of a national screening programme that must be borne upfront is often high and needs to contend with other competing priorities. Hence, it requires political decisions based on sound evidence of the cost-effectiveness of screening to make a financial commitment to initiate these programmes. However, such commitment is not a one-off but a continuous undertaking of birth reduction aiming for zero new thalassaemia birth when the budget allows.

Cao et al., reported that the global prevalence of thalassaemia is still high.[1] In 2013, 56,000 children were born with thalassaemia major, where approximately 30,000 were affected by beta-thalassaemia, and 3,500 succumbed perinatally from the debilitating hydrops foetalis syndrome. The global incidence of symptomatic individuals is estimated to be one in 100,000.[2] Kadhim et al.,[3] stated that thalassaemia occurs in 4.4/10,000 live births. As reported in 2017 by Origa R, approximately 68,000 children are born with various thalassaemia syndromes yearly.[4]

Countries with high prevalence have made impressive thalassaemia prevention and control. There are several approaches adopted, and studies have reported the various outcomes of these initiatives at the country level. A successful initiative has been demonstrated in North Cyprus. They started with high carrier rates of thalassaemia. Two studies in 1946 and 1973 reported thalassaemia carrier rates of 18.2% and 15%, respectively. North Cyprus made an unprecedented decision to introduce a screening programme. It started in 1979 to screen high-risk families. The following year, pre-marital screening became legally required in 1980. Prenatal diagnosis began with foetal blood sampling techniques in 1984. Later in 1991, DNA techniques replaced foetal blood sampling. Since the prenatal diagnosis began, affected birth rates have dropped dramatically, compared to an average of 18-20 cases per year. North Cyprus has earned the honour as the first country to achieve a satisfactory reduction in carriers and thalassaemia major newborns. Between 1991 and 2001, only five thalassaemic babies were born, or only one every 2-3 years. No thalassaemic babies were born between 2001 and 2007.[5] In another study reported by Şanlidağ et al.[6], since the mandatory pre-marital screening in North Cyprus, there was a successful depletion of new thalassaemic babies born since 2001.

A study in Iran has shown the importance of screening, in which those who were positive carriers have voluntarily cancelled their marriage intention. Between 2002 and 2006,

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the average rate of marriage cancellation among the carrier couples was reported at 53%, with a minimum rate of 38% in 2003 and a maximum rate of 69% in 2006.[7]

The importance of initiating a thalassaemia screening and prevention programme is to lighten the cost burden of treating primary thalassaemia patients, which need lifelong treatment, including life-long blood transfusions and chelation therapy. In addition, complete blood counts, iron studies, and heart, kidney, and liver tests are required. Often cases need to be referred to medical specialists such as paediatricians, haematologists, and endocrinologists. Such follow-ups incur additional charges, such as hormonal investigations for growth monitoring.[8] In 2011, a decade ago, the total expenses throughout life for a patient with thalassaemia major were projected to be GBP219,608.[9] In Malaysia, Shafie et al.,[10] reported that the lifetime cost per Transfusion Dependent Thalassaemia (TDT) patient was USD606,665 extracted from the sum of lifetime healthcare costs. The price has increased many folds since, with these patients living longer and the increased treatment cost.

To the best of our knowledge, systematic reviews on thalassaemia screening, birth reduction initiatives, and relation to the programme's cost have not been reported. This study provides a comprehensive summary of the retrieved literature through a systematic search of various screening of thalassaemia initiatives in several countries. Therefore, the shared birth outcomes and costs incurred or saved can help administrators make decisions based on high-quality evidence of the intervention costs and outcomes. In addition, the quality of the included literature was evaluated by employing the updated PRISMA 2020 and Mixed Methods Appraisal Tool (MATT) method.

MATERIALS AND METHODS

Review Protocol

A systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) Statement guidelines of quantitative and qualitative studies.[11] The authors used several methods to identify synonyms and related terms for four main keywords related to screening programmes, birth, cost and success and narrowed them down to topics like thalassaemia screening and birth reduction initiatives, including prevalence, burden, challenges, impact, declining, prenatal, children, born, success and family. These keywords were combined with search functions and Boolean operators in databases like Scopus and Web of Science and identified 5,425 potential articles. The authors also manually searched databases like Science Direct, Emerald, Taylor Francis, Springer Link and Sage Journals.

Formulation of Research Question

The formulation of the research question was based on PICO, a tool that assists authors in developing a relevant research question for the review. PICO is based on three main concepts: Population or Problem, Interest and Context. Based on these concepts, the authors have included three main aspects in the review, namely thalassaemia patients (Population), treatment cost-effectiveness (Interest) and screening programmes (context) which then guide the authors to formulate its main research question—What are the costs and the outcomes of the thalassaemia screening programme in reducing the birth incidence of thalassaemia?

Screening and Eligibility Criteria

The eligible inclusion criteria of the literature met the following: (a) Thalassaemia patients as the target population; (b) articles expressing comparison birth numbers after the intervention was implemented; (c) the study contained economic evaluation where results expressed with the cost comparison between pre-and post-intervention as well as (d) articles published between 1992 until December 2022. In addition, non-original articles (e.g. drafts, case studies, conference posters or abstracts) were excluded. This systematic review only considered full-text articles in the English language.

RESULTS

Figure 1 illustrates the identification process of studies collected and screened. In total, 5,425 were from electronic databases. We removed 4,905 articles, including non-published articles, those published before 1984, non-English and did not meet the criteria by browsing the titles and abstracts. This includes another 21 duplicates, which then came to 499 full-text articles eligible for review. Further article exclusion was made on those which do not focus on the four main keywords used for searching the database, based on screening the title (n=260), abstract (n=65) and content (n=6). Another 118 articles were excluded after quality appraisal. Finally, 50 full-text studies were included and analysed in this review.

Quality Appraisal

With the assistance of two co-authors, the corresponding author assessed each article's methodological and analytical rigour. Each article was carefully read, focusing on its methodology section and the analysis undertaken. Then, guided by the Mixed Methods Appraisal Tool, the authors scrutinised the articles, searching for the consistency of the sampling and analysis undertaken (e.g., random sampling vs inferential analysis). Each article was assessed based on five criteria with three options provided in presenting their answers: 'yes', 'no' and 'do not know/cannot tell'. The articles were included in the review if they passed at least three criteria. All decisions on the assessment were based on mutual agreement.

Study Characteristics

The essential characteristics of the 50 included full-text studies are reported in Table I. These studies were performed in 21 different countries, including Iran (n=9),[12-20] Malaysia (n=4),[9-10,20,21] and Cyprus (n=3),[5,6,23]. Iraq,[3,24] Canada,[25,26] Turkey,[27,28] Israel,[29,30] Sri Lanka,[31,32] Thailand,[33,34] Greece,35,36 India,[37,38] Palestine,[39,40] and Italy[41-42] each contributed two publications. Publications from the remaining countries each have a single citation:, Singapore,[43] Omani,[44] Saudi Arabia,45 France,[46] Taiwan,[47] Maldives[48] and China[49]. Iran, Malaysia, and Cyprus accounted for most studies, between three to eight articles.

Table I: Articles included for review according to themes

No.	Author	Year	Countries	Title	Themes
1.	Longinotti et al.[41]	1994	Italy	A 12-year preventive program for β-thalassaemia in Northern Sardinia	Theme 1: Prevalence
2.	Haque et al.[21]	2015	Malaysia	Thalassaemia: Level of awareness among the future health care providers of Malaysia	
3.	Ibrahim et al.[22]	2020	Malaysia	Observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry	
4.	Gholam Hasan et al.[12]	2013	Iran	Frequency of Thalassaemia in Iran and Khorasan Razavi	
5.	Miri et al.[13]	2013	Iran	Thalassaemia in Iran in the last twenty years: the carrier rates and the births trend	
6.	Canatan[27]	2011	Turkey	Haemoglobinopathy prevention program in Turkey	
7.	Kattamis et al.[54]	2020	-	Changing patterns in the epidemiology of β-thalassaemia	
8.	Şanlidağ et al.[6]	2016	Cyprus	Prevalence of Thalassaemia Trait & Iron Deficiency Anaemia during Infancy in 2011–2013 in a Thalassaemia Prevalent Region: North Cyprus	
9.	Wong et al.[43]	2009	Singapore	Prevalence of haemoglobinopathies in Singapore	
10.	Safdar et al.[48]	2017	-	Economic Burden of Thalassaemia on Parents of Thalassaemic Children: A Multi-Centre Study	
11.	Mustafa et al.[55]	2020	Maldives	Genetic epidemiology of beta-thalassaemia in the Maldives: 23 years of a beta-thalassaemia screening program	
12.	Voskaridou et al.[35]	2019	Greece	National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality	
13.	Bozkurt[5]	2007	Cyprus	Results from the North Cyprus thalassaemia prevention program	Theme 2: Birth reduction
14.	Koren et al.[29]	2014	Israel	Prevention of β-thalassaemia in Northern Israel-A cost-benefit analysis	
15.	Alkindi et al.[44]	2010	Omani	Forecasting hemoglobinopathy burden through neonatal screening in Omani neonates	
16.	Kadhim et al.[3]	2017	Iraq	Prevalence, incidence, trend, and complications of thalassaemia in Iraq	
17.	Saffi et al.[28]	2015	Turkey	Exploring the Effectiveness of Mandatory Premarital Screening and Genetic Counselling Programmes for β-Thalassaemia in the Middle East: A Scoping Review	
18.	Samavat et al.[14]	2004	Iran	Iranian national thalassaemia screening programme	
19.	Chern et al.[56]	2006	-	Impact of a national β-thalassaemia carrier screening program on the birth rate of thalassaemia major	Theme 3: Screening
20.	Saba et al.[42]	2017	Italy	Non-invasive prenatal diagnosis of beta-thalassaemia by semiconductor sequencing: a feasibility study in the Sardinian population	
21.	Sirdah et al.[40]	1998	Palestine	Screening secondary school students in the Gaza Strip for β-thalassaemia trait	
22.	Langlois et al.[25]	2010	Canada	Carrier screening for thalassaemia and hemoglobinopathies in Canada	
23.	Esmaeilzadeh et al.[15]	2021	Iran	Major Thalassemia, Screening or Treatment: An Economic Evaluation Study in Iran	
24.	AlHamdan et al.[45]	2007	Saudi Arabia	Premarital screening for thalassaemia and sickle cell disease in Saudi Arabia.	
25.	Colah et al.[37]	2017	India	Burden of thalassemia in India: the road map for control	
26.	Cowan[23]	2009	Cyprus	Moving up the slippery slope: mandated genetic screening on Cyprus.	
27.	Karimi et al.[17]	2007	Iran	Premarital screening for beta-thalassaemia in Southern Iran: options for improving the programme	
28.	Lena-Russo et al.[46]	2002	France	Outcome of a school screening programme for carriers of haemoglobin disease	
29.	Mitchell et al.[26]	1996	Canada	Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassaemia disease carriers in high schools	
30.	Rahbari et al.[20]	2014	Iran	Dropouts and social determinants of health; policy for the prevention of school dropout, qualitative study of the causes and interventions	
31.	Tarazi et al.[39]	2007	Palestine	Obligatory premarital tests for β-thalassaemia in the Gaza Strip: evaluation and recommendations.	
32.	Jameela et al.[9]	2011	Malaysia	Thalassaemia screening among students in a secondary school in Ampang, Malaysia	

Table I: Articles included for review according to themes

No.	Author	Year	Countries	Title	Themes
33.	Ostrowsky et al.[57]	1985	-	Cost-benefit analysis of a thalassaemia disease prevention program	Theme 4: Programme cost
34.	Voskaridou et al.[36]	2012	Greece	A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births	
35.	Shafie et al.[10]	2021	Malaysia	The economic burden in the management of transfusion-dependent thalassaemia patients in Malaysia from a societal perspective	
36.	Ginsberg et al.[30]	1998	Israel	Cost-benefit analysis of a national thalassaemia prevention programme in Israel	
37.	Ghotbi et al.[18]	2005	Iran	Evaluation of the national health policy of thalassaemia screening in the Islamic Republic of Iran.	
38.	Riewpaiboon et al.[33]	2010	Thailand	Economic burden of beta-thalassaemia/Hb E and beta-thalassaemia major in Thai children	
39.	Sattari et al.[19]	2019	Iran	The financial and social impact of thalassaemia and its treatment in Iran	Theme 5: Treatment Cost
40.	Ho et al.[47]	2006	Taiwan	Financial burden of national health insurance for treating patients with transfusion-dependent thalassaemia in Taiwan	
41.	Pankaj et al.[38]	2010	India	Expenditure to Treat Thalassaemia: An Experience at a Tertiary Care Hospital in India	
42.	Karnon et al.[31]	2000	Sri Lanka	Thalassaemia in Sri Lanka: implications for the future health burden of Asian populations.	
43.	Karnon et al.[58]	2012	-	Lifetime Cost-Utility Analyses of Deferasirox in Beta-Thalassaemia Patients with Chronic Iron Overload	
44.	Mutar et al.[24]	2020	Iraq	Thalassaemia Prevention Program in Iraq: Cost-Effectiveness and Applicability	Theme 6: Cost-effectiveness
45.	Esmaeilzadeh et al.[16]	2016	Iran	Economic burden of thalassaemia major in Iran, 2015	
46.	Leech et al.[59]	2018	-	Use and misuse of cost-effectiveness analysis thresholds in low-and middle-income countries: trends in cost-per-DALY studies	
47.	Bang et al.[60]	2014	-	Cost-effectiveness analysis: a proposal of new reporting standards in statistical analysis	
48.	Amarasinghe et al.[32]	2022	Sri Lanka	Redesigning new policy options for thalassaemia prevention in Sri Lanka	
49.	Laoarayawat et al.[34]	2020	Thailand	Effectiveness Analysis of Prenatal Screening Program for Thalassaemia Between Semi-accelerated Screening Step and Current Program	
50.	Leung et al.[49]	2004	China	Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong	

Data Extraction and Analysis

The articles were thematically analysed, given that the review relied on diverse research designs, presenting the best ways to integrate the differences by performing a qualitative synthesis.[50] While several qualitative syntheses could be applied, the present review relied on the approach suggested by Flemming et al.,[51] who stressed the suitability of thematic synthesis for synthesising data from diverse research designs due to its flexible mode. Furthermore, thematic analysis attempts to identify and notify the pattern of existing studies by detecting any similarities or relationships that could exist in available data.[52] In this review, the thematic synthesis was based on the steps suggested by Kiger et al.[53]

Firstly, agreement and disagreement were quickly settled via discussion among the authors. Based on this process, all authors agreed that all selected articles passed the minimum quality requirement regarding the methodology and analysis. Secondly, the generation of codes was conducted. Data were organised at a granular and specific level. During this stage, selected articles and extracted any data related to the main research question. The third process involved theme generation. The researchers practised inductive coding frameworks and attempted to note any interests, similarities, and connections between the extracted data. The themes developed were associated with the original data and reflective of the entire data set.[52] During this process, six main themes were developed.

Developing the Themes

The thematic analysis was undertaken on 50 articles. It resulted in six main themes (a) prevalence and thalassaemia burden, (b) birth reduction, (c) screening methods, (d) programme cost, (e) treatment cost and (f) cost-effectiveness. Based on the results, six themes provided answers to the main research question of this SLR, 'how do the thalassaemia screening programmes help reduce the birth and cost burden of the country?' The background of the selected studies is explained in the following section.

Findings from the review concluded six thematic areas in analysing the success of thalassaemia screening in reducing birth. The six main themes are (1) prevalence and thalassaemia burden, (2) birth reduction, (3) screening

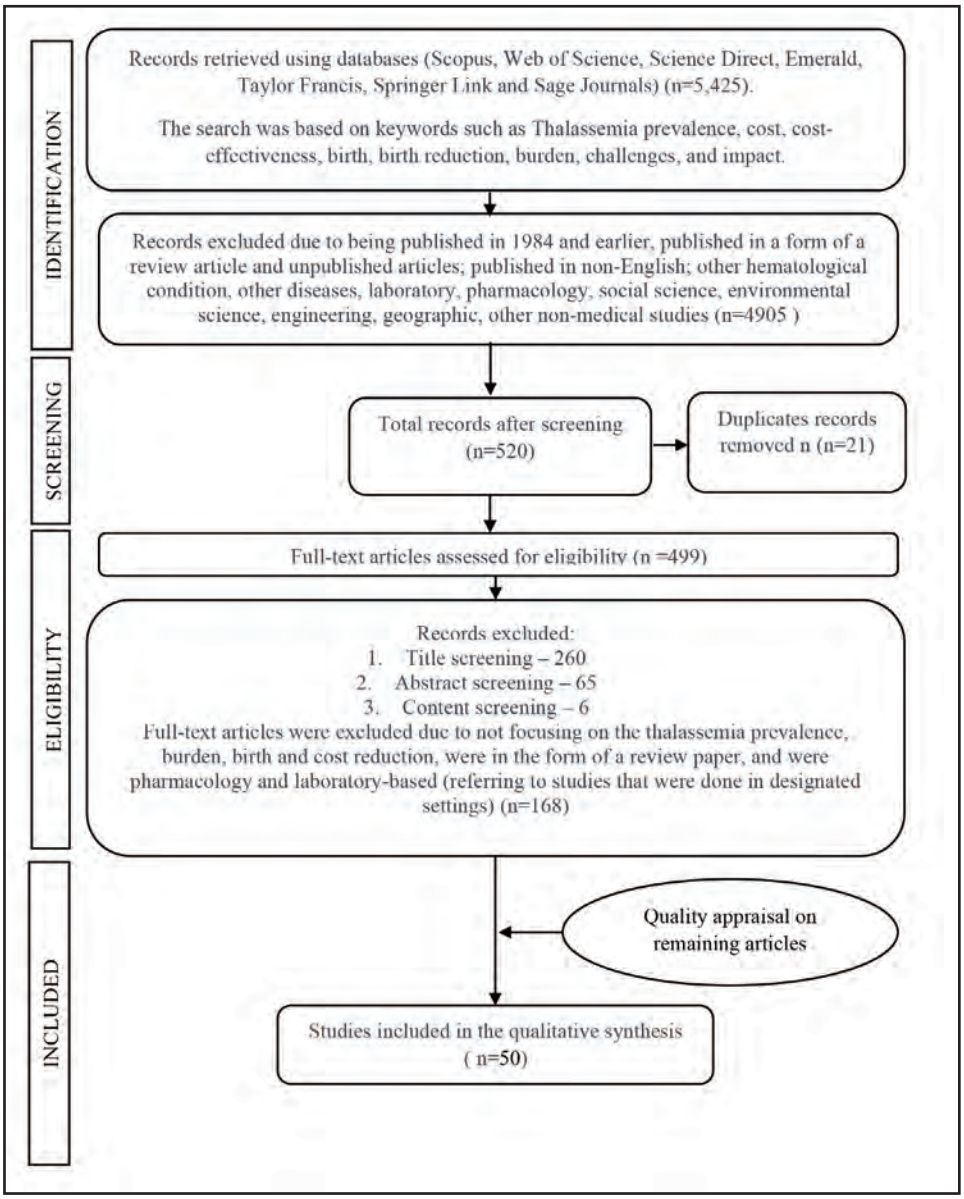

Fig. 1: PRISMA flow diagram

methods, (4) programme cost, (5) treatment cost and (6) cost-effectiveness. Figure 2 represents the six thematic areas and the articles associated with each category. A detailed listing of the articles included is provided in Table I.

DISCUSSION

Prevalence of Thalassaemia

The prevalence of a condition is the percentage of people in a population who have that condition at a particular time or over a period of time. In this systematic review, the authors have analysed the prevalence of thalassaemia in several countries, including Cyprus, Iran, Maldives, Malaysia, Sardinia, Singapore, and Turkey. It provides a more objective measurement and mitigation effectiveness and facilitates ease in comparing data from different populations.

The prevalence of thalassaemia is exceptionally high in certain parts of the world, known as the 'thalassaemia belt'.[61] This belt includes countries in the Mediterranean region, Southeast Asia, and parts of Africa where the frequency of carriers of the thalassaemia gene is high. In these countries, thalassaemia is a significant public health issue, as the high prevalence of carriers in the population leads to a high incidence of the condition.

Global

Thalassaemia, a debilitating inherited haematological disorder, was first identified in the early 1900s in the United States and Italy. As screening for the condition has become more widespread, the number of people diagnosed with thalassaemia has increased. According to Origa R,[4] thalassaemia is highly prevalent, with an estimated 1.5% of the global population carrying the gene for the condition. This translates to around 80 to 90 million carriers worldwide.

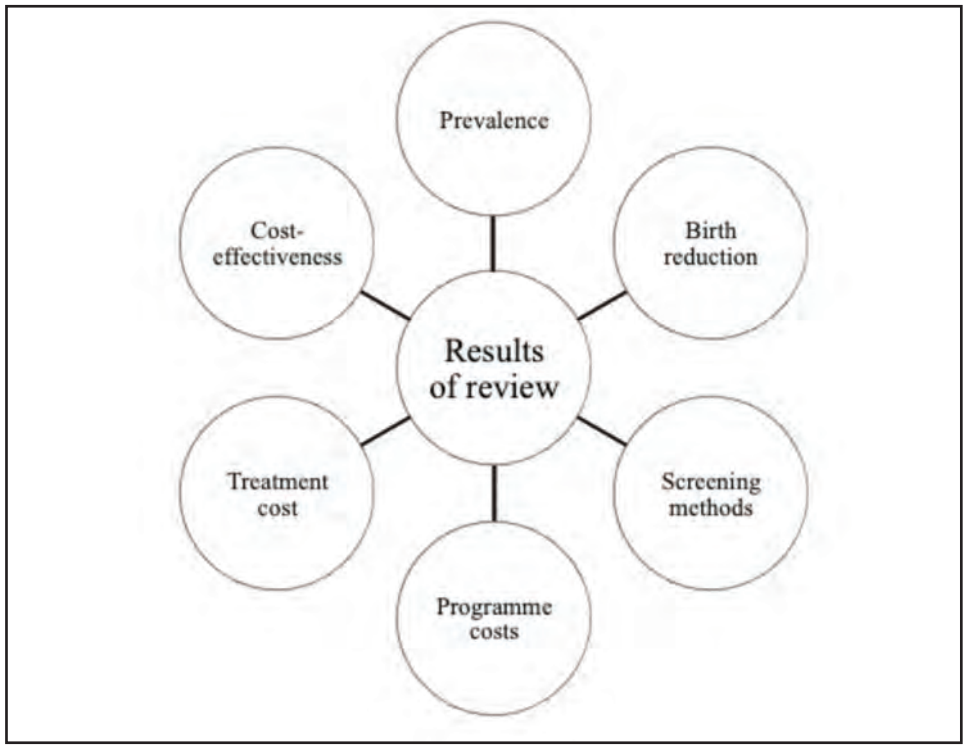

Fig. 2: Six thematic areas

Thalassaemia is prevalent in many parts of the world, particularly in the 'thalassaemia belt', which stretches from the Mediterranean basin to Southeast Asia. It is also found in Central Asia, Southern China, and the Far East, as well as in North Africa and South America. The highest carrier frequency has been reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia (3-5%).[62]

The Mediterranean

In the Mediterranean region, thalassaemia is especially prevalent in countries such as Cyprus, Greece, Italy, Iran and Turkey. The prevalence of carriers in these countries ranges from 10% to 25%.[27,54] This high prevalence is due to the high frequency of carriers in these populations. In addition, consanguineous marriages (marriages between close relatives) are more common in these countries, increasing the risk of thalassaemia.

Published articles on thalassaemia in North Cyprus, conducted in 1946 and 1973, found frequencies of 18.2% and 15%, respectively.[6] A more recent study conducted in 2013 found a frequency of 7.9%, representing a 50% decline in the prevalence of thalassemia compared to the 1973 study. In Sardinia, Cao et al. reported that the estimates of thalassaemia prevalence in Sardinia were between 10.3% and 15.7% and attributed that the factors of high prevalence may be related to genetic and demographic factors.[1] It was also reported that the 10.3% prevalence was contributed by a high prevalence of HbE-beta-thalassaemia in four regions of Sardinia.[41] In Iran, the overall prevalence was much lower at 4% in 2013.[12] However, in some localities, the Ministry of Health in Iran has reported that the provinces of Hormozgan, Sistan and Baluchistan, and Mazandaran have an average prevalence of 9%, 8.5%, and 8%, respectively.[13]

Maldives

The Maldives has a high prevalence of thalassaemia, with a reported rate of 18% of the population.[55] This is a significant number considering the smaller size of the Maldivian population. In addition, the migration of Maldivian citizens to other countries has also contributed to the prevalence of thalassaemia in those countries. For example, there is a reported prevalence of 16% in Cyprus and 3-8% in the populations of China, Bangladesh, and Malaysia.[48]

South-East Asia

The prevalence of thalassaemia in Asian countries is significantly lower. For example, according to Wong et al.[63], the prevalence of thalassaemia carriers in Malaysia is 4.5-6%. It was noted that individual perception and stigma towards thalassaemia could contribute to the rising prevalence of the condition. Approximately 4.5% of the population is estimated to be carriers of beta-thalassaemia in Iran.[13] Moreover, the prevalence rate of beta-thalassaemia in Malaysia is similar to Iran and higher among Malay ethnicity.[22] In Singapore, the nearby neighbour also reported in 2009 a 3.7% prevalence for thalassaemia and other haemoglobinopathies.[43]

Thalassaemia Birth Reductions

It is difficult to provide a specific percentage of thalassaemia birth reductions worldwide, as the incidence of thalassaemia varies widely from region to region and depends on several factors, including the prevalence of the thalassaemia gene in a population, access to genetic testing and counselling, and the availability and uptake of prevention measures.

The Mediterranean Region

In the Mediterranean region, Thalassaemia preventive initiatives have successfully lowered the number of Thalassaemia major births in Italy, Greece and Cyprus. Between 1972 and 1984, the preventative programme in Italy had a success rate of 62%, whereas Greece's had a success rate of 52%.[48] In its first epidemiological study, Cyprus reported that the prevalence of thalassaemia carriers was 17.2%.[64] Implementing a thalassaemia prevention programme in Cyprus, including compulsory premarital screening and prenatal diagnosis, has led to a significant decline in thalassaemia births. A 2011-2013 study found that the prevalence of thalassaemia trait in infancy in the region was around 7.9%, with no new cases reported since 2001.[5] The success rate of the prevention programme in Cyprus has been estimated to be 96%.[48] To hasten the reduction initiative, the government implemented a legal provision for premarital screening tests to be made compulsory for couples. This policy effectively reduced the birth rate of thalassaemic babies in the Turkish Cypriot population.[5] In Sardinia, an expanded thalassaemia screening programme was conducted among adults in the province of Sassari from 1980 to 1991. The programme screened 6.3% of adults, and the results showed that the prevalence of beta-thalassaemia was 15.7%.[41] In Iran, a study published by Samavat et al.[14] showed that the intervention programme significantly decreased the birth rate of thalassaemia patients from 1998 to 2002. The success rate of the thalassaemia prevention programme was estimated to be 82.3% in 2009, with the number of newborn thalassaemia patients falling from 1087 cases in 1989 to 239 in 2009.[13] It is estimated that, in Turkey, an average of four or five therapeutic abortions would be performed each year, given a 25% incidence of affected foetuses. These measures effectively reduce the number of thalassaemia births in other countries and could potentially be successful in reducing the number of thalassaemia births in Turkey.[28]

Therapeutic abortion, often a subject of intense ethical debate, intersects with the principle of non-maleficence, or the obligation to do no harm. In the realm of medical ethics, the decision to terminate a pregnancy for therapeutic reasons requires careful consideration of both the physical and mental well-being of the mother, as well as potential harm to the foetus.[65] Discussions surrounding non-maleficence in the context of therapeutic abortion often delve into deeply held beliefs about the sanctity of life, autonomy, and the rights of both the mother and the unborn child. Some argue that allowing therapeutic abortions upholds the principle of non-maleficence by preventing greater harm to the mother,[66] while others contend that terminating a pregnancy violates the inherent dignity and right to life of the foetus.[67] Ethical considerations in this realm necessitate a nuanced understanding of medical, social and cultural factors, as well as a commitment to balancing the well-being of all involved parties.

For the thalassaemia programme, therapeutic abortion pertains to the deliberate termination of a pregnancy upon the diagnosis of thalassaemia in the foetus, either through prenatal testing or during antenatal care. Various countries adopt distinct approaches to define the terms and conditions under which termination is permissible. For instance, in Germany, abortions are permitted up to the 22nd week for foetal abnormalities after a 3-day waiting period, and up to the 12th week with counselling or physician approvals, while recent Cyprus legislation allows abortions up to 12 weeks with a mandatory psychological consultation.[68] In Israel, abortion regulations have undergone multiple revisions, allowing termination under the age of 18 with the approval of an appointed committee, potentially extending beyond 24 weeks.[68,69] Iran permits selective abortion up to 15 weeks as part of its prevention programme, resulting in a significant reduction in the prevalence of new thalassaemia cases.[70,71] Similarly, Turkey allows termination at a younger gestational age of 10 weeks, with the possibility of extension based on stringent health criteria.[72]

Therapeutic abortion has been integrated into the national prevention and intervention programmes of several countries, including Cyprus, Israel, Iran and Turkey. Despite facing criticism from religious factions or segments of the population regarding abortion, these nations have achieved significant reductions in new thalassaemia births.[28] Remarkably, there is no evidence to suggest that these countries intend to reverse their decision on therapeutic abortion. This underscores the effectiveness of incorporating abortion services into comprehensive healthcare strategies aimed at mitigating the prevalence of genetic disorders like thalassaemia.

Asian Region

From 2007 to 2011, there were 1483 affected births in Malaysia, which decreased to 214 between 2017 and 2018. This declining trend is likely due to increased public awareness and initiatives like free early population screening and health education. Prenatal screening for thalassaemia is also available upon request in government hospitals, though the screening rate remains low.[22] Since 2019 the National Prevention and Control programme has been expanded to include 14-year-old. The success of the reduction will be appreciated once this cohort starts to give birth. In Singapore, the success rate of the thalassaemia prevention programme was found to be 90%, with the number of new cases falling from an average of 37 per year in the 1980s to less than five per year in 2000.[43]

Screening Methods

Thalassaemia screening was first introduced in the early 1970s as a national initiative.[56] Over the decades, the growth of innovation and technology has seen techniques made simpler with lesser steps and faster turnaround time with greater accuracy. As a result, several types of screening have been on the market. However, in this review, the selected articles were able to find only three types of screening that were adopted which include (1) pre-pregnancy / in the early stage of pregnancy/pre-gestational screening/pre-marital, (2) prenatal diagnosis/antenatal diagnosis, (3) population screening approach.

Pre-conception Screening

Pre-pregnancy screening for preventing beta-thalassaemia and other hemoglobinopathies has been done in Northern Israel since 1987.[69] Pregnant women were screened on their

first visit to community Mother and Child Health Clinics, and subsequently, the husbands of the affected women were also screened. Other nations have laws requiring premarital thalassaemia testing for all couples before marriage approval, including Iran since 1991.[14,73] The pre-marital screening began in Cyprus as early as the 1980s and was mandated by the Cypriot Orthodox Church for Greek Cypriots before they could get married.[23] In 1993, this form of mandatory pre-marital thalassaemia screening also continued to be a policy in the Palestinian Territories in 2000,[39] and Saudi Arabia in 2003.[45] The Taiwan government conducted a National Screening Programme to reduce the birth rate of thalassaemia major. It involves obstetricians routinely screening pregnant women's complete blood count.[74] These nations implemented the programme backed by legal provisions to reduce the prevalence of thalassaemia.

Pre-natal Diagnosis

As early as 1974, Greece started their prenatal diagnosis screening under the Greek National Prevention Program for thalassaemia and other haemoglobinopathies. The National Prevention Program provides services through the general hospital, which consists of a specific haematology unit and a prenatal diagnosis unit.[75] Both pre and post-test counselling are essential for prenatal diagnosis programmes to eliminate irrational fears among people, particularly regarding stigmatisation. It also helps individuals and families at risk come to terms with the situation and consequences of the disorder.[37] Cyprus started legislating 1980 mandatory thalassaemia carrier screening, and a prenatal diagnosis programme was started by the end of 1984.[76] In Sardinia, the married couples who were carriers of the c.118C4T variant in the HBB gene were counselled for prenatal diagnosis via peripheral blood screening.[42] In Israel, couples at risk of having affected offspring are referred for genetic counselling and prenatal testing starting in 1987.[69]

Student Screening

Thalassaemia screening is also offered to secondary high school students. A thalassaemia screening programme was conducted in India among high school students between 1984-1988, and 5682 students were screened. Out of which, 153 (2.7%) were found to have beta-thalassaemia.[78] In a similar programme on screening over 25,000 high school students in Montreal, Canada, from 1972 to 1992, 693 students were detected as carriers (1 in 36). The carriers identified in the high school programme remembered their status, had their partners tested and opted for prenatal diagnosis if required.[25,79] Another study from the Marseille region in France evaluated a screening programme for secondary school children from 1978 to 1985.[80] The study assessed the partner's uptake for testing by sending a letter along with an anonymous questionnaire to all the carriers. In total, 86% of them knew they had to test their partners. Six carrier couples were identified, and four requested prenatal diagnosis. Cross-sectional studies were conducted in Palestine[40] and Malaysia.[9] This screening exercise showed that thalassaemia carriers are common and are feasible to carry out a screening programme for secondary high school students and will impact the prevalence of thalassaemia.

Treatment and prevention are complementary and can reduce healthcare expenditure, particularly in the case of thalassaemia, to improve quality of life. Practical preventive approaches have demonstrated success in the above countries described. However, screening programs need to be backed by public education and a combination of regulatory frameworks to provide people with the information they need to make wise decisions and guarantee that people are not subjected to discrimination because of the findings of their tests. The screening programme is usually packaged with genetic counselling for individuals at risk, offers carrier testing to individuals with a family history of the disorder and provides prenatal diagnosis for pregnant women at risk of having a child with thalassaemia.

Programme Cost

The lifetime healthcare costs of transfusion-dependent thalassaemia from countries (such as the United Kingdom, United States, Italy, Iran, Thailand, Taiwan and India vary between USD363,149 and USD720,201.[10] This may include home infusion service, chelating agent, stay in the hospital, operation, outpatient visits, laboratory tests and therapist.[30] In addition, studies have demonstrated that screening and prevention initiatives reduce the number of newborns with thalassaemia but are also cost-effective compared to providing people with thalassaemia who depend on blood transfusions with lifelong supportive care.[10]

The World Health Organization committee emphasised a significant economic value that would could result from preventing thalassaemia in several European populations with a high incidence of the disease.[80] In Cyprus, the annual cost of operating the screening and prenatal diagnosis programme is about the same to the cost of treatment of existing patients for five years. Meanwhile, in Sardinia, it is estimated that a reducing the prevalence of thalassaemia by 90% would allow the establishment of a prevention programme to be paid off in three years from the start of the services; thereafter, the total cost of treatment would steadily reduce to one-fifth of the projected cost of treatment over the next five years.[57]

Thalassaemia Prevention Programme operates differently in different countries. Without prevention, annual treatment costs could rise to over USD150 million annually for one birth in Iran. The estimated annual cost of prevention in Iran is USD7,730 compared to the cost of treating thalassaemia, which is USD12,387.[16] Referring to the annual number of 1251 births of thalassaemia major here, the cost difference of USD3 million was saved by implementing the prevention screening programme.

The Israel National Screening Programme for Thalassaemia costs USD900,197, amounting to USD4.6 million for 13 homozygotes born. However, if the screening programme is not implemented, the lifetime medical care costs for 26 homozygotes would amount to USD7.5 million.[30] In another study by Koren et al., the cost of preventing one affected newborn was USD63,660 compared to USD1,971,380 for treating a patient for 50 years (mean annual cost: USD39,427).[29] Therefore, the preventative programme still benefits USD76 million over ten years, even after deducting the cost of the prevention programme (USD413.80/year). Therefore, each case prevented could cover the cost of screening and prevention programmes for 4.6 years.

The annual cost of carrier screening for thalassaemia trait in Montreal was USD26,648. The total undiscounted sum of these costs for the first 25 years of treatment is USD176,426 or USD7,057/per patient per year.[57] In Greece, there are several programmes in place to prevent the occurrence of thalassaemia. The total annual cost of the prevention programme is calculated to be only about EUR1,400,000, while the cost of treatment per thalassaemia major patient was approximately EUR2,229-4,371 per month.[36] In Iraq, it was reported in 2016 that each patient's management cost is USD1,428-3,785/month, an average of USD2,606.5 per month, with USD31,278 per year. The incidence of thalassaemia in Iraq in 2015 was 335 patients. If these cases were prevented, assuming the value of the preventive measures of USD63,660 would be much more cost-effective than case management.[24]

Treatment Costs

The various journals that reported treatment costs showed varying approaches in presenting their findings. Therefore, from the selected journals discussed in this paper, the contents for this theme on treatment costs are grouped into six ways how the cost are reported, namely, (a) prevention of one affected child/patient, (b) the annual cost of prevention, (c) cost per patient per month, (d) the annual cost per patient, (e) average treatment cost, (f) the lifetime cost of treatment and the lifetime cost of treatment.

As the treatment modalities vary between countries, which depends on the health infrastructure and resources employed, the policy or clinical guidelines that are followed, and the GDP for the different years, this article does not intend to compare costs between countries directly. Instead, it will share the findings to explain the costs incurred. The treatment cost is vital information as they significantly impact the economy and costs to the family problems, notwithstanding the societal problems that the disease may compound.

A study conducted by Koren et al., in Israel reported that preventing one case of affected β-thalassaemia new-born was only one-third the cost of treatment; USD 63,660 compared to USD 1.981,380 for treatment of beta-thalassaemia for over a lifetime of 50 years.[29] We could not find another country to compare this cost. However, Ostrowsky et al. reported that the annual cost of carrier screening for the thalassaemia trait in Montreal was USD26,648, which appeared to be far cheaper than reported by Koren et al.[29,57] In Greece, a study in 2012 showed the total annual cost of the prevention programme is calculated to be only about EUR1,400,000 or USD1,089,340 (Av exchange rate 1 USD in 2012:0.7781 EUR).[36] The scope of the screening prevention programmes in these countries may be very different to make a fair comparison.

Greece has started focusing on thalassaemia screening and treatment since the 1970s. This has given a positive outcome, given medical and supportive management, and it has provided an overall survival rate of 65% at the age of 50 years. Voskaridou et al.[36] 2012 estimated the cost of treatment per thalassaemia major patient to be approximately EUR2,229-4,371 per month. In Iraq, Mutar et al., shared that each patient's management cost is USD1,428.00-3,785.00/month; this includes blood transfusion and drugs, as this is calculated for life.[24]

In India, de Silva et al. found that the treatment cost includes costs of blood and its preparation, chelating agents, essential investigations, and hospital visits, and calculated that the average cost of treatment for the patient for a year is about INR175,000 (USD2,465).[81] A recent Indian study showed that the treatment of TDT was estimated to be USD1,135 annually.[82] While this study showed that in Thailand, the annual average cost of treatment from a societal perspective was approximately USD950 (at the year 2005 prices), of which 59% was direct medical cost, 17% was direct non-medical cost, and 24% was indirect cost. The total undiscounted costs for the first 25 years of treatment are USD176,426 or USD7,057 per patient-year.[33]

Taiwan reported that the undiscounted lifetime cost of treating TDT study was estimated at USD561,208.[47] Shafie et al., noted that in Malaysia, a TDT patient is expected to incur. Therefore, the lifetime cost of TDT patients is estimated to be USD 606,665.[10] In the United Kingdom, Karnon et al. in 1999, reported that the undiscounted lifetime cost of treating a beta-thalassaemia major patient was estimated to be GBP803,002.[31] However, when the costs were discounted at a rate of 6%, the lifetime cost was reduced to GBP219,068.

Cost-Effectiveness of Prevention

From the various papers screened on thalassaemia, it was noted that many studies commonly reported, among others, prevalence, the cost and financial burden, and the screening methods, though not all were covered in one paper. Most sparingly, however, are studies on cost-effectiveness. Cost-effectiveness analysis compares the costs and outcomes of different strategies to determine which provides the greatest value, responding to the need to manage health care's significant economic burden and high costs of medical interventions.[60] This review found only a few studies that have reported the cost-effectiveness of the intervention programme at the country level. As the approaches reported between these countries are dissimilar, this review will share the findings of each study in their respective countries.

Israel started their screening and intervention programme in 1987. In 2014, Koren et al., conducted a cost-effectiveness study and found that the cost of preventing one affected newborn was USD63,660 compared to the treatment cost, which is almost 30 times more, USD1,971,380 for the treatment of a patient for 50 years (the mean annual cost: USD39,427).[29] His study concluded that USD88.[5] million of net savings to the health budget over 10 years prevented 45 new thalassaemia cases, plus an additional USD76 million over 10 years after deducting the cost of the prevention programme (USD413,795/year).[83]

Iran started the minor thalassaemia screening programmes and intervention in 1997, a decade after Israel. It was a solid political commitment requiring thalassaemia screening test results before approval for official marriage registration. Esmaeilzadeh et al., compared the cost of screening and treatment.[15] The study found that screening techniques prevented 26.97 patients with thalassaemia major, and the

cost of prevention for each birth was estimated to be USD32,624 compared to the treatment cost of USD136,532 per year. For context, Koren et al., reported significantly lower mean annual treatment cost of USD39,427 in Israel.[29]

In Hong Kong, Leung et al., conducted a cost-effectiveness study that retrospectively reviewed the prenatal screening programme from 1998 to 2002 and compared the screening cost against the treatment cost.[49] The study estimated that the total expenditure for the screening programme would cost HKD10.0 million, much less than the postnatal service costs, which were HKD40.4 million for 18 beta-thalassaemia major foetuses if they were born. Hong Kong started with an indirect approach of serial ultrasound and, subsequently, invasive tests for definitive diagnosis in participating prenatal clinics. This approach provided 100% sensitivity and a low false positive rate of 2.9%. The study recommended that running a universal prenatal screening programme in an area where both β-thalassaemia and α-thalassaemia are prevalent is cost-effective. In addition, the indirect approach can effectively avoid an invasive test in unaffected pregnancies.

In 2020, a study in Thailand conducted the cost-effectiveness of prenatal screening thalassaemia between two methods; a semi-accelerated screening programme was compared with the current conventional programme. It was found that the new modality could detect many more cases 34 versus only eight by the current programme. Thus, the expected costs of the semi-accelerated screening programme were higher than the current programmes, with a difference of THB609.[29] and THB462.44.[34] However, the cost-effectiveness of the benefits or potential future reduction of the cases was not discussed.

Amarasinghe et al., have comprehensively analysed the cost-effectiveness of thalassaemia prevention in Sri Lanka.[32] In 2022, the study was conducted in five districts where the screening programme was implemented. The intervention package involved three elements: a) an education programme, b) nationwide screening and c) antenatal screening with the termination of pregnancy. The study found that the previous policy of promoting 'safe marriages' could reduce one thalassaemia major birth whilst the new policy package of a, b and c were able to minimise births by 14, 35 and 48, respectively. Although the cost per prevention was USD 20,084 through termination of pregnancy, the authors suggested that a less legal approach to the intervention is taking an island-wide screening that will cost USD22,324 and mass education costing USD12,420. As a combo approach, improving uptake and making it less objectionable to the community is cost-effective.

LIMITATIONS

The decline in thalassaemia births can also be attributed to the declining population growth rate, and the success of birth control programmes can mask the actual decline of the programme during the same period. This can be shown by the study in Iran, which showed a declining trend in the number of birth cases of thalassaemia during the period from 1989 to 1995, when the prevention programme was not yet in place. Since the implementation of the prevention programme in 1996, the rate of thalassaemia births has declined.[13] The thalassemia prevention programme in Iran has impacted reducing the number of thalassaemia births in the country. Health decision-makers must continue reviewing and improving the programme to reduce the number of affected patients. Similar scenarios may be common in many countries. However, thus far, no studies have shown the rate of decline in isolation by the two effects, namely birth control and the screening programme.

CONCLUSION

This systematic review found that the thalassaemia intervention and control programmes in selected countries have reduced thalassaemia births. They include countries in the Thalassaemia Belt and others with a high prevalence of thalassaemia traits. North Cyprus, Iran, Iraq, Greece, Turkey, Oman and Canada have shared their success in reducing the incidence between 50% and 90%. North Cyprus, in particular, with no reported new cases in recent years. Previous studies supported the various intervention programmes showing treatment cost-savings if effective prevention has been implemented. However, treatment costs range from 23 to 65 times more expensive than the cost of the screening programme.

This systematic review concluded that countries that have invested in screening and control programmes could enjoy savings on treatment costs and an appreciative reduction in thalassaemia incidence and morbidity. However, the screening modality must be tailored to the local culture and respect the religious values and sensitivities to earn a generous response from the community. The main limitation was the matching of the incidence, cost of prevention and treatment, which are collated from different authors for different years for the country understudied.

DECLARATIONS

Ethics approval and consent to participate.

No ethical approval was required for the conduct of this systematic literature review as it is based on published research and does not involve any new studies of human participants or animals performed by any of the authors.

Availability of data and material

Data sharing does not apply to this article as no datasets were generated during the current study.

Declaration of Conflicting Interests

The authors declared no competing or conflict of interest concerning this article's research, authorship and publication.

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Authors' contributions

All authors have reviewed the manuscript, believe it represents valid work, and approve it for publication. In addition, all authors participated in the research design, the research performance, data analysis and manuscript writing.

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Statistical properties of auditory behaviour outcome measures for children with hearing loss: a scoping review

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ABSTRACT

Introduction: Various evaluation tools have been developed to track the growth of auditory-related behaviours of children with hearing loss during intervention. However, the reliability and validity of currently available outcome measures remain uncertain due to the lack of information on their psychometric properties. A lack of reliable outcome measures may jeopardise intervention quality and affect these children's listening skills progression. This scoping review aims to explore the mechanics of producing or developing an outcome measure either completely new or adapted from the original version that is considered as having robust statistical properties.

Materials and Methods: A scoping review was conducted across four databases (PubMed, ScienceDirect, Scopus and Google Scholar). The included articles were written in English, published between January 2010 and June 2023, and specific to predefined keywords. Two independent reviewers screened and selected the final papers using the PRISMScR checklist. A code framework was created to extract information about the publications and conducted by one reviewer. The results were reported using descriptive statistics and narrative synthesis.

Results: The final analysis were conducted on 22 articles out of 452 articles screened. The review identified seven outcome measures presented in various languages. The outcome measures found were the Auditory Behaviour in Everyday Life (ABEL), Functional Listening Index for Paediatric (FLI-P), Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), Integrated Scales of Development (ISD), LittlEARS Auditory Questionnaire (LEAQ), Parent's Evaluation of Aural/Oral Performance in Children (PEACH), Parent's Evaluation of Aural/Oral Performance in Children Diary (PEACH Diary), Teachers' Evaluation of Aural/Oral Performance in Children (TEACH) and Parent's Evaluation of Aural/Oral Performance in Children Plus (PEACH+). A total of 13 studies focused on translating, adapting and validating an outcome measure while the remaining investigations validated either the translated or original version of the outcome measures. All original instruments were developed in English and among Western culture, except for the LEAQ which was designed in the German language and for the German population. The outcome measures identified were translated and adapted into Spanish, Turkish, Persian, Hebrew, Arabic, Malay, Yoruba, Polish, Swedish, Hindi, Portuguese, Kannada and Mandarin.

Conclusion: All studies performed an extensive evaluation of psychometric properties and feasibility studies to produce an excellent quality of auditory-related behaviour outcome measure for clinical use with the intended population. A new outcome measure, FLI-P, was found to be clinically useful for the primary provider of learning to listen and spoken language training for children with hearing impairment in Malaysia, i.e., the speech-language therapists.

KEYWORDS:
Paediatric, young children, infant, hearing impairment, hearing loss, audiological outcome, questionnaire

INTRODUCTION

Conventionally, behavioural or objective audiological assessments through audiometric tests were used to measure the accessibility towards sounds post-hearing intervention. However, these assessments have limitations in explaining how a child with hearing loss uses and integrates the sounds they hear in everyday life.[1,2] Subjective tests, such as questionnaires, diaries and structured interviews, serve as the outcome measures that can address this gap by assessing the auditory-related behaviours in real-world listening environments.[2-4] These measures require the parent(s) and/or teacher(s) observational opinion to quantify a child's auditory or oral performance in everyday listening situation.[2-4] Therefore, tracking a child's skill development and progress using a valid auditory-related behaviour outcome measure is a necessary routine for professionals involved in intervention using spoken language, considering the significant impact of hearing towards language and speech development.[5-6] These professionals include the early interventionists, auditory-verbal therapists, speech language therapists (SLTs), audiologists and/or teachers of the deaf.[5-7]

Standardised and valid auditory-related behaviour outcome measures are important for accurately monitoring the progress and outcomes of children with prelingual hearing loss receiving listening intervention.[7] Numerous auditory

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inventories have been developed for measuring a child's listening skills post-intervention.[3,4,8] Many of them were developed for English-speaking populations, which may not be appropriate for different populations and cultural contexts.[9,10] However, the selection of auditory behaviour measurement tools to assess the intervention outcomes by Malaysian early intervention professionals is influenced primarily by the accessibility, usability, comfort and familiarity of the tools.[1] This scenario results in considerable variability and disparities in reporting outcomes, even among professionals within the same field, particularly among SLTs—the primary providers of early intervention for spoken language in Malaysia.[1] As the evaluation and reporting processes are time-consuming, such evaluation and tracking are not regularly done at specified intervals.[6,7] This imposes significant difficulties for clinicians to track a child's progress and needs for further intervention to improve outcomes. Furthermore, Moodie et al.,[11] emphasised the importance of having an evidence-based age-appropriate outcome measure for effective collaboration between professionals and parents in forming decisions for a child's individualised rehabilitation plan.

Reliable data tracking on functional listening skill progress is fundamental in guiding intervention for better language outcomes while providing support for further decisions and directions in the rehabilitation plan.[1,3,5,6] Therefore, the present scoping review aimed to explore the mechanics of producing or developing an outcome measure either completely new or adapted from the original version that is considered as having robust statistical properties i.e. those with good test-retest reliability, internal consistency, validity and responsivity.[3]

For the purpose of readability of this paper, the authors will use the term auditory-related behaviours to represent behaviours as defined in the Erber's (1984) auditory hierarchy and also more complex spoken language levels that are the consequences of sophisticated auditory functioning.[1]

MATERIALS AND METHODS

Information Sources

A systematic search of four databases, i.e., PubMed, ScienceDirect, Scopus and Google Scholar was performed between 14 June to 21 June 2023 for articles published between published between January 2010 and June 2023. Searched terms and strategies were developed and supported by two researchers in this study. Keywords and related MeSH terms associated with the audiological measure, paediatric, infant, young child, listening outcome, questionnaire, hearing loss and hearing impairment with various combinations were used in the search domains depending on the search settings in selected databases.

Searching Techniques

The scoping review was conducted based on Arksey and O'Malley's five stages of methodological framework.[12] It involved five stages as described below.

Stage 1: Identifying the research questions

1. What are the auditory-related behaviour outcome measures that are available for professionals who provide listening intervention to children with hearing loss all over the world?
2. What are the reliability and validity status as well as the method used in measuring the statistical qualities of the selected auditory-related behaviour outcome measures?

Stage 2: Identifying relevant studies

A systematic electronic search was conducted on four databases, i.e., PubMed, ScienceDirect, Scopus, and Google Scholar between 14 June to 21 June 2023 for articles published between January 2010 and June 2023. Searches on the grey literature with specific keywords of known research studies were conducted to expand the chances to obtain more data. Any unpublished articles or studies regarding auditory-related behaviour outcome measures, as well as non-English published articles were excluded to minimise potential disputes in the reviewed data. The keywords of outcome measures, outcome evaluation, audiological, paediatric, infant, young child, listening outcome, questionnaire, hearing loss and hearing impairment with various combinations were used in the search domains depending on the search settings within the selected databases. The search results were uploaded onto a reference management software and any duplicates were removed. The remaining abstracts were imported into a citation account shared by all researchers.

Stage 3: Study selection

Two reviewers were involved in the screening of studies against the eligibility criteria. All studies included in this review must be published between 2010 to 2023 in the English language. The outcome measures used within this study should meet the following criteria, in which they must: 1) Measure the auditory-related behaviour in real-world listening environments; 2) Provide the psychometric qualities data and 3) Include the skills of children aged between 0 and 6 years. Each study was independently evaluated by both reviewers and an initial screening of titles and abstracts was performed to remove studies that were not within the scope of this review. It was followed by another independent screening and review of the publications' titles, abstracts and full-text copies by both reviewers to eliminate articles that failed to meet the inclusion criteria. Findings from both reviewers were further contrasted during a single discussion conference two weeks after the screening process. A third and fourth reviewer were contacted for further consultation and review of the whole study.

Stage 4: Charting the data

Two evaluators independently reviewed each article and constructed a data extraction form using the Microsoft Excel software (Microsoft, Inc, Redmond, WA, USA). Only articles that satisfied the inclusion criteria were captured in the data extraction form. Following a discussion about whether the charted articles answered the research questions, both evaluators and the third reviewer agreed to finalise the data, which included the author(s), publication year, study location, research objective(s), methodology, subjects/participants, reliability and validity data and conclusion.

Stage 5: Collating, summarising, and reporting results
All articles were gathered, reviewed and reported on the following themes: (1) Study characteristics, (2) Outcome measure description and features, (3) Validity and reliability data and (4) Conclusion of the study. The results section contains a detailed summary of the data acquired from this review. A fifth reviewer was contacted to review the whole report and provide consultation to enhance the readability of the paper.

RESULTS

The literature search generated 545 results across four databases, namely PubMed (239 results), Scopus (65 results), ScienceDirect (180 results) and Google Scholar (61 results). Any duplicates were deleted, resulting in 452 articles related to the research topic that were further screened using the established inclusive criteria. The title and abstract screening of these articles produced 32 articles that were chosen for full-text retrieval; however, three articles were unable to be retrieved. Following the full-text screening, seven articles were judged to be ineligible for inclusion, leaving a total of 22 articles that were included in this scoping review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 28 was used as the guideline for this scoping study (Figure 1). Different methods, testing procedures and analyses were identified across studies. Therefore, a narrative approach was employed to report the findings of all studies included in the scoping review.

Characteristics of the Studies
The scoping review found that 13 studies were aimed towards translating and adapting the original version of an auditory-related behaviour outcome measures followed by a psychometric properties evaluation of a newly produced measure.[2,4,13-23] The outcome measures identified in these studies were translated and adapted into different languages, including Spanish,[13,16,24] Turkish,14 Persian,[15,22,25] Hebrew,[17] Arabic,[17] Malay,[4,18,23] Yoruba,[19] Polish,[26] Swedish,[27] Hindi,[20] Portuguese,[28] Kannada,[2] and Mandarin.[21,29] All of the original outcome measures were produced in English except for one which was produced in German.[24] The age range of children investigated in these studies was between three months and 18 years of age as the selection of participants was based on the indicated age range of each outcome measure. The characteristics of all studies included in this review are listed in Table I.

The other nine studies targeted towards validating either the original version[6,30,31] or the translated and adapted version of an outcome measure.[14,24-27,29] This review found three out of nine studies had different goals in their validation study which led to different methods and research designs. The first study investigated the feasibility of LittlEars Questionnaire (LEAQ), as a screening tool to identify abnormal hearing development in children, especially in situation where objective measures might not be available.[31] As such, part of the original measure was removed to shorten the measure and to suit the age range of infants involved in the study (i.e., ≤12 months old). The second study aimed to modify their already translated measure, Mandarin version of Infant-Toddler Meaningful Auditory Integration Scale, which was found unsuitable to be used with children who did not receive auditory intervention in their previous study.[29] The investigators used a combination of item response theory (IRT) and classical test theory (CTT) to modify the measure before evaluated its psychometric properties. Another study attempted to modify, validate and compare the new translated version of Persian- Auditory Behavior in Everyday Life Questionnaire with the previously translated version.[25]

Outcome Measures Description and Features
Eight audiological outcome measures were identified from the current review. The Functional Listening Index for Pediatric (FLI-P) by Davis et al., was the newest outcome measure, published in 2022, and employed to measure the auditory-related behaviour of children aged zero to six years old.[6] Six studies were found to use the outcome measure that catered the age range from infancy through childhood, namely the Parents' Evaluation of Aural/Oral Performance of Children Rating Scale (PEACH), Parents' Evaluation of Aural/Oral Performance of Children Diary (PEACH Diary), Parents' Evaluation of Aural/Oral Performance of Children Rating Scale Plus (PEACH Plus)[4,13,14,23,30] and two studies chose the Auditory Behaviour in Everyday Life (ABEL).[25,28] Furthermore, 11 studies used the LittlEARS Auditory Questionnaire (LEAQ),[2,16,17,19-22,24,26,27,31] which was developed for children aged 0 to 24 months. Other outcome measures identified in this review were the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) which was used by one study,[29] the Integrated Scales of Development (ISD) which was used by one study,[18] and the Teachers' Evaluation of Aural/Oral Performance of Children (TEACH) which was also used by one study.[15] IT-MAIS was developed for older infants through childhood years, whilst ISD was designed for children aged 0 to 48 months. Another outcome measure, TEACH, was meant for older children who have attended early intervention centres, preschool or school throughout their childhood years. All outcome measures aimed at measuring the auditory-related behaviour or functional listening skills in real-world listening situations; except for IT-MAIS which only has a few items that cover beyond the sound detection and discrimination level. Additionally, FLI-P, LEAQ and ISD were identified to measure the skills over time and provide the steps for development. However, only FLI-P enlisted the items for measuring advanced auditory-related behaviour skills in older children. The description of outcome measures in this study is provided in Table II following the format presented in Bagatto et al.[3]

Translation and Adaptation Process
All 13 translation studies used the forward-backward translation method with a different number of translators of varying qualifications and backgrounds. At least one translator either from the research team or outside professional was recruited to perform the forward translation. The same scenario was observed in the backward translation process. The harmonisation stage where expert panel reviewed the translated and adapted version was mentioned in all studies with different number and background of panels, except for one study that did not describe this stage in the article.[21] Different methods of validating the content and face of the new measures were also discovered and specifically mentioned only by five studies[14-16,18,22] while other

translation studies did not mention this type of validity stage. Table III outlines the characteristics of the translation and adaptation process for each study in this review.

Validity and Reliability Data

Internal consistency

All thirteen translation studies measured the internal consistency using the Cronbach's alpha value and reported high internal consistency which indicates good reliability of the translated scale measurements. In contrast, only five out of nine validation-only studies – Persian ABEL, Polish LEAQ, Brazilian Portuguese PEACH rating scale, original English PEACH, Mandarin IT-MAIS and Swedish LEAQ – measured internal consistency value using Cronbach's Alpha value[25,26,28-30] while the remaining studies did not mention this value in their report.

Construct validity

Nine translation studies showed good construct validity by reporting high item and total score correlations[2,4,13,14,16,20-23] which indicate a robust positive relationship between an individual item within the test and the overall score of the entire instrument. However, only five out of nine validation-only studies reported the same high construct validity which were calculated using either the regression analysis,[30] factor analysis,[25] item-total correlation,[26,29] and/or difficulty indices.[24,26]

Criterion-related validity

For concurrent validity where the correlation between age and total scores was measured, nine translation studies reported good concurrent validity[2,4,15-17,19-22] while only five validation-only studies reported good concurrent validity.[6,24,27,28,31] These studies found a positive correlation between age and total scores, indicating that older participants tended to score higher on the test. This suggests that the instrument demonstrates good concurrent validity because its scores align well with participants' ages. The elevated sensitivity and specificity were mentioned in three translations[13,14,17] and five validation-only studies6,[25-28] which indicates that the translated instrument is effective in accurately identifying both individuals with and without the hearing impairment. The measurement was performed by measuring the correlations of total scores with different variables (type, degree and laterality of hearing loss, type of device, additional needs, age at device fitting, duration of hearing aids usage before cochlear implantation, chronological age, age at implant activation, age at hearing aid fitting, responses to sounds while using hearing aids before cochlear implantation, and daily usage of hearing aids). High convergent validity was observed in two studies.[27,29] Five studies reported high predictive accuracy in either detecting a child with hearing loss or predicting the future outcome of the auditory-related behaviours of the child.[6,20-22,31]

IV- Test-retest reliability

Out of thirteen translation studies, seven performed test-retest reliability correlation at different intervals ranging from seven days to as long as four weeks and good correlation values were reported by all studies.[2,4,14,15,17,20,23] Five validation-only studies also performed the test-retest reliability with varying number of administration times and intervals with good test-retest reliability.[6,25-27] The number of test administration and duration of test intervals ranged from once in 15 days to 12 in two years (two months interval).[27] High correlations indicate that the measurements taken at different points in time were consistent and stable, suggesting that the tested measure maintained its reliability over time.

V- Index of difficulty

Only two studies measured the difficulty index of their instruments.[21,26] One is the translation study of Mandarin version of LEAQ by Wang et al.,[21] and the other is the validation-only study of Polish version of LEAQ by Obrycka et al.,[26] Both studies reported a good range of difficulty index between 0.31 to 1.00 and 0.52 to 1.00 respectively. The ranges indicated that the items in the instruments were arranged nearly in ascending order of difficulty, with the 'easiest' items representing basic auditory-related behaviour skills and the most 'difficult' ones representing advanced auditory-related behaviour skills.

VI- Normative curves

Eight translation studies plotted the normative curves using the linear regression analysis[4,16,17,19-23] with one study of Hebrew and Arabic version of LEAQ mentioned distinctively about the similarities of their normative curve with the original normative curve using Pearson's correlation.[17] Normative curve was only reported in two validation-only studies in which one study on the original PEACH rating scale by Bagatto et al., compared the produced curve with the previously generated curve[30] and the other study of Swedish LEAQ plotted the predictive growth curve using the linear regression mixed model.[27] Table IV provides an overview of reliability and validity data for all translation studies whilst Table V provides the validity and reliability data of the validation-only studies .

Conclusion of Studies

From the review, 21 out of 22 studies concluded that the outcome measures that were translated, adapted, and/or validated in their studies were reliable and valid in measuring the auditory-related behaviour development of children with specific listening and language environment.[2,4,6,13-17,19-31] They were also useful for clinical practice to monitor and evaluate the effectiveness of auditory-related behaviour skills intervention among children with hearing loss. However, the study of the Malay version of ISD is recommended by the authors to be utilised only as a guide to monitor communication development rather than as an assessment tool.[18] Another study of LEAQ in Swedish mentioned that their studied measure assessed auditory-related behaviours and language skills to a large extent rather than just the audition alone.[27] A study about the suitability of the shortened version of LEAQ as a screening tool was promising as it was easily implementable and served as a good alternative in countries with no objective screening instruments available.[31] Furthermore, a study that modified the existing translated measure found that the combined use of IRT and CTT provided a powerful means to modify psychometrically robust scales.[29] A study which aimed towards validating a newly developed outcome measure, FLI-P, found that the scores derived from their measure can guide

Table I: The characteristics of studies included in the review.

Author	Outcome measure	Country (Language)	Version	Age (Number of subjects)
Bagatto et al.[30 (a)]	PEACH rating scale	Canada (English)	Original	2 to 83 months (n=59 TH)
Bravo-Torres et al.[13 (a)]	PEACH rating scale	Spain (Spanish)	Translation & Adaptation	4 to 18 years (n=297 TH)
Davis et al.[6 (a)]	FLI-P	Australia (English)	Original	0 to 72 months (n=543 HI; 32 TH)
Eroğlu et al.[14 (a)]	PEACH rating scale	Turkiye (Turkish)	Translation & Adaptation	3 to 12 years (n=120 HI)
Fatahi et al.[15 (a)]	TEACH rating scale	Iran (Persian)	Translation & Adaptation	2 to 11 years (n=40 TH; 42 HI)
García et al.[16 (a)]	LEAQ	Spain (Spanish)	Translation & Adaptation	19 to 24 months (n=215 TH)
Geal-Dor et al.[17 (a)]	LEAQ	Israel (Hebrew & Arabic)	Translation & Adaptation	9 to 24 months (n=70 TH (Hebrew) + 97 TH (Arabic); 42 HI)
Hani et al.[18 (a)]	ISD	Malaysia (Malay)	Translation & Adaptation	16 to 30 months (n=12 TH)
Kayode et al.[19 (a,c)]	LEAQ	Nigeria (Yoruba)	Translation & Adaptation	6 to 24 months (n=423 TH)
Obrycka et al.[26 (a)]	LEAQ	Poland (Polish)	Translation & Adaptation	6 to 22 months (n=122 HI)
Oryadi et al.[25 (a)]	ABEL	Iran (Persian)	Translation & Adaptation	1 to 6 years (n=113 HI)
Persson et al.[27 (a)]	LEAQ	Sweden (Swedish)	Translation & Adaptation	16 to 59 months (n=25 TH)
Prakash et al.[20 (a)]	LEAQ	India (Hindi)	Translation & Adaptation	6 to 24 months (n=59 TH; 41 HL)
Quar et al.[4 (a)]	PEACH Diary	Malaysia (Malay)	Translation & Adaptation	3 months to 13 years (n=74 TH)
Quar et al.[23 (a)]	PEACH+ rating scale	Malaysia (Malay)	Translation & Adaptation	4 months to 7 years (n=157 TH)
Levy et al.[28 (a)]	ABEL	Brazil (Portuguese)	Translation & Adaptation	4 to 14 years (n=18 HI)
Schaefer et al.[31 (a)]	LEAQ	German (German)	Original	0 to 60 months (n=47 (6 HI))
Spitzer et al.[24 (a)]	LEAQ	Spain (Spanish)	Translation & Adaptation	5 to 21 months (n=50 TH)
Umashankar et al.[2 (a)]	LEAQ	India (Kannada)	Translation & Adaptation	1 to 24 months (n=67 TH; 20 HI)
Wang et al.[21 (a)]	LEAQ	China (Mandarin)	Translation & Adaptation	4 to 24 months (n=157 TH)
Yang et al.[29 (b)]	IT-MAIS	China (Mandarin)	Translation & Adaptation	0 to 24 months (n=450 TH+HI)
Zarifian et al.[22 (a)]	LEAQ	Iran (Persian)	Translation & Adaptation	Below 24 months (n=240 TH)

(a) Measures auditory-related behaviour skills
(b) Partially measures auditory-related behaviour skills
TH – Typical hearing; HI – Hearing impaired

Table II: The description of outcome measures found in this review.

Outcome measure	Number of items	Response format	Scoring format	Age range	Factors assessed	Developer/Reference Author
ABEL	24	7-point scale	Subscale and overall averages	4 to 14 years	Aural-oral, auditory awareness, social/conversational	Purdy et al.[36]
FLI-P	64	Mostly/Rarely	Total of 'mostly' responses	0 to 6 years	Six phases of auditory behaviours, organised in developmental hierarchy	Davis et al.[4]
IT-MAIS	10 probes	Parental observation and reports via structured interview	Overall score (based on examples given)	Older infancy through childhood	Vocalisation behaviour, alerting to sounds, meaning from sound	Geier[34]
LEAQ	35	Yes/No	Total of 'yes' response	Birth to 24 months	Three categories of auditory behaviours, organised in developmental hierarchy	Kuehn-Inacker et al.[37]
PEACH Diary	13	5-point rating scale	Subscale and overall percentages	Infancy through childhood	Use of devices and loudness discomfort, listening in quiet and noise, phone use, environmental sounds	Ching et al.[35]
PEACH Rating Scale	13	5-point rating scale	Subscale and overall percentages	Infancy through childhood	Use of devices and loudness discomfort, listening in quiet and noise, phone use, environmental sounds	Ching et al.[8]
PEACH+ Rating Scale	12	5-point rating scale	Subscale and overall percentages	Infancy through childhood	Use of hearing devices, listening in quiet situations, listening in noisy situations, ease of demonstrating listening behaviour in different situation	Ching et al.[8]
TEACH	11	5-point rating scale	Subscale and overall percentages	Older children through childhood	Hearing aid use, loudness discomfort, communication in quiet and noise, environmental sounds	Ching et al.[8]

Table III: The translation and adaptation characteristics of each study.

Study-Author	Forward translation	Harmonisation I	Backward translation	Harmonisation II	Content and face validity
PEACH Rating Scale, Bravo et al.[13]	3 native speakers	1 PT, 1 linguist, 1 audiologist. 5 audiologists (different countries; same language)	1 native English Speaker	NA	20 parents
PEACH Rating Scale, Eroğlu et al.[14]	2 audiologists, 1 linguist, 1 PT	2 audiologist, 1 ENT	1 linguist	1 linguist reviewed	40 parents
TEACH Rating Scale, Fatahi et al.[15]	Followed the International Quality of Life Assessment Project Protocols				10 audiologists, 10 teachers
LEAQ, García et al.[16 (a)]	1 PT, 1 psychometrician, 1 SLT	Reviewed with researchers	1 PT, 1 psychometrician, 1 SLT	NA	3 SLT, 30 parents
LEAQ, Geal-Dor et al.[17]	Authors	NA	Authors	1 SLT	NA
ISD, Hani et al.[18]	Authors	3ST, 1 linguist, 1 psychologist, 2 students ST	Authors	10 lecturers SLT	3 parents
LEAQ, Kayode et al.[19]	1 linguist	NA	1 linguist	NA	3 ENT physician
LEAQ, Prakash et al.[20]	4 audiologists	Authors	2 audiologists	Authors	2 SLT
PEACH Diary, Quar et al.[4]	Author	2 audiologists	1 audiologist	NA	6 parents
PEACH+ Rating Scale, Quar et al.[23]	1 English language teacher	Reviewed with researcher (audiologist)	2 translators	1 linguist & 1 audiologist	NA
LEAQ, Umashankar et al.[2]	5 audiologists	Authors	3 audiologists	Authors	3 SLT
LEAQ, Wang et al.[21]	No specific number and flow mentioned				
LEAQ, Zarifian et al.[22 (a)]	1 ST, 1 audiologist, 1 psychologist	Experts review (CVI)	1 SLT	Developer representative	NA

PT – Professional translator, SLT – Speech-language therapist, (a)Cognitive interviewing

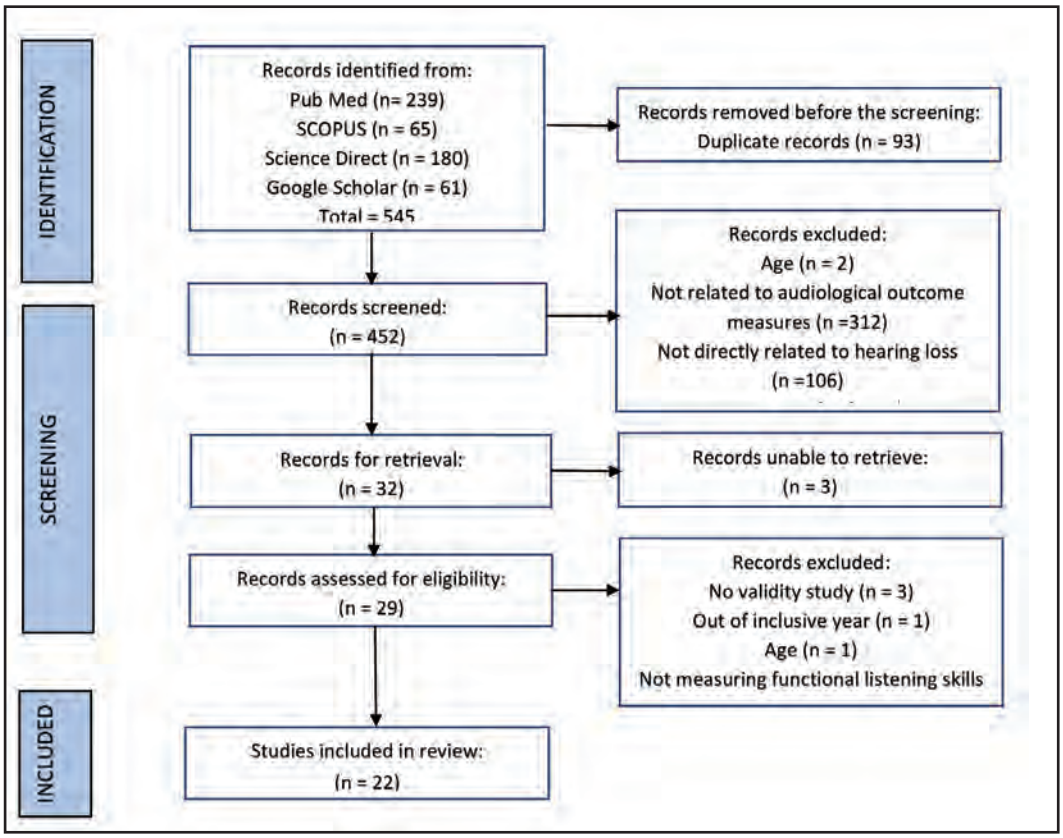

Fig. 1: Flow of the literature search and screening process.

Table IV: The validity and reliability data of translation studies.

Author	Outcome measure	Cronbach's α (Internal consistency)	Test-retest reliability	Validity
Bravo-Torres et al.[13]	PEACH rating scale	0.93	NA	Strong content validity Good construct validity Elevated sensitivity and specificity Good discriminant validity
Eroğlu et al.[14]	PEACH rating scale	0.94	r=0.949 (3 to 4 weeks interval)	Good construct validity High sensitivity and specificity
Fatahi et al.[15]	TEACH rating scale	0.98	r=0.87 to 0.97; (2 weeks interval)	High content validity index Good discriminant validity Good concurrent validity Strong correlation between P-TEACH and P-PEACH
García et al.[16 (a)]	LEAQ	0.93	NA	Good construct validity Good concurrent validity Good Discriminant validity
Geal-Dor et al.[17 (a)]	LEAQ	Hebrew – 0.96 Arabic – 0.95	F (1.09,7.62)=9.468, p=0.015	Good concurrent validity Good convergent validity Good discriminant validity
Hani et al.[18]	ISD	16-18 months – 0.87 19-24 months – 0.63 25-30 months – 0.63	NA	Good content and face validity
Kayode et al.[19 (a)]	LEAQ	0.90	NA	Significant predictive accuracy Good discriminant validity Good concurrent validity
Prakash et al.[20 (a)]	LEAQ	0.96	Z=–1.81, p > 0.05 (7 to 9 days interval)	High predictive validity Good discriminant validity Good concurrent validity
Quar et al.[4 (a)]	PEACH Diary	0.93	χ=- 0.6; range=- 0.7 to - 3.3 (2 weeks interval)	Good construct validity (high item-total correlations)
Quar et al.[23 (a)]	PEACH+ Rating Scale	0.90 (frequency of auditory behaviour), 0.93 (ease of listening behaviour)	t(9)=-1.327 to -0.429, p>0.05) (2 weeks interval)	Good construct validity (high item-total correlations)
Umashankar et al.[2(a)]	LEAQ	0.75	Z=0.94, p > 0.05	Fair concurrent validity Good construct validity
Wang et al.[21 (a)]	LEAQ	0.94	NA	High predictive accuracy Good construct with original validity Good discriminant validity Good concurrent validity Good range of index difficulty
Zarifian et al.[22 (a)]	LEAQ	0.96	NA	Good predictive accuracy Good concurrent validity Good construct validity

[(a)] Has normative data

and support discussion and intervention decisions and also bridge the gap between information from audiological assessments and language measure.[6] Out of all the studies reviewed, nine have produced normative curves in which the professionals may plot on to track the child's development of the auditory-related behaviours.[4,16,17,19-22,27,30]

DISCUSSION

The Available Auditory-Related Behaviour Outcome Measures

This scoping review found eight different instruments in various languages that are useful for measuring the auditory-related behaviour development, and subsequently monitoring the intervention outcome in children with hearing loss. Although these outcome measures differ in their features and clinical indications, all of them demonstrated good reliability and validity values, indicating their ability to measure what it is supposed to measure with consistent findings and results. In general, the knowledge about clinical features of each outcome measure is important in guiding the clinicians to choosing and determining the most feasible and viable instrument for their clinical use.[3] The PEACH Diary, PEACH Rating Scale, PEACH+ Rating Scale, IT-MAIS, LEAQ and FLI-P were identified to be appropriate to measure the auditory-related behaviours from infancy, with LEAQ narrowing its focus of development only up to 24 months old.[31] The ABEL and TEACH on the other hand, were more suitable for pre-school children, preferably from 4 years old. The PEACH Rating Scale, PEACH+ Rating Scale, LEAQ and FLI-P showed good clinical feasibility and responsivity due to their administration via interview-observation or past-self-recollection, rated by either the clinicians or parents. In contrast, for both PEACH Diary and IT-MAIS, consideration for their practicality and ease of use has to be made because

Table V: The validity and reliability data of validation-only studies.

Author	Outcome measure	Cronbach's α (Internal consistency)	Test-retest reliability	Validity
Bagatto et al.[30 (a)]	PEACH rating scale	0.78	NA	Good construct validity Good concurrent validity High sensitivity and specificity
Davis et al.[4]	FLI-P	NA	Steep inclines in listening trajectories over time (3 to 4 months interval)	Good construct validity Good concurrent validity Good predictive validity Good discriminant validity High sensitivity and specificity
Obrycka et al.[26]	LEAQ	0.83	Significance difference in auditory development (Test intervals – 1,3,6,9,12 months old)	Good construct validity Good range of difficulty index Good concurrent validity
Oryadi et al.[25]	ABEL	0.96	df=5, F=35.67, p value < 0.001	Good construct validity
Persson et al.[27 (a)]	LEAQ	NA	Every 2 months for 1 year F (3.894, 93.467) =368.304, p<0.001 Every 2 to 4 months for 2 years	Good convergent validity - LEAQ and McArthur-Bates CDI. Weak to no correlations with PEACH LEAQ. Measure language skill rather than audition.
Levy et al.[28]	ABEL	>0.7	p>0.05 (no significant difference) (15 days interval)	Good concurrent validity Poor to negative sensitivity
Schaefer et al.[31]	LEAQ	NA	NA	Good predictive accuracy for detecting hearing loss Low predictive accuracy for detecting speech delays and language development
Spitzer et al.[24 (a)]	LEAQ	0.95	NA	Good construct validity Good criterion validity Good discriminant validity
Yang et al.[29]	IT-MAIS	0.92	NA	High convergent validity Good construct validity Good concurrent validity

[(a)] Has normative data

of their open-interview style administration format as described in the review by Bagatto et al.[3] Another useful features for a clinician when tracking a child's skill developmentally is the normative curve, that is represented as the trajectory graph of scores. These graphs which are included in PEACH, PEACH+ Rating Scale and FLI-P, provide an over-time tracking framework to the intervention team for informed decision making and determining intervention direction. Further scrutiny revealed that FLI-P is the only outcome measure that enlists a wide range of auditory-related behaviour skills in a real-world listening environment. FLI-P sequences these skills hierarchically, starting from early sound awareness phase up to advance open-set phase, making it extensively different from the other measures in this review.[6] This plus point feature was found to give greater impact clinically in guiding SLTs to set the intervention aims, and discuss the intervention outcome with the parents and other professionals on the intervention team. Another almost similar measure to FLI-P is the ISD. The ISD adopts the milestone checklist-like presentation for five different developmental areas simultaneously,[18] rendering a much simpler and generalized auditory-related behaviours checklist compared to the FLI-P. This feature reduces ISD practicality in monitoring a child's progress clinically as well as in setting therapy focus.

The Validity and Reliability Status and Methods in Measuring the Statistical Properties

The selection of outcome measures for translation and adaptation is determined by the clinical indication of the population in addition to the validity and feasibility evidence provided by the developer.[33] As recommended by Hall et al,[32] investigators should choose a measure that requires minimal changes with relevant and equivalent concept of interest across sources and target countries where it will be used for translation and adaptation studies. Despite the variations in the types of validity and reliability measurements reported by each study, the primary focus remains on validating the newly developed instrument to ensure its clinical feasibility for the targeted population. Majority of the studies reviewed consistently reported the internal consistency values of their measures. Internal consistency indicates the strong reliability of the translated scale measurements.[3] All translation study reported high Cronbach's Alpha value for their internal consistency measurement whilst only a few of the validation-only studies did. This discrepancy in reporting highlights the importance of consistently evaluating and reporting internal consistency across studies to ensure transparency and reliability in the assessment of measurement instruments. Construct validity assesses the degree to which a measurement tool accurately measures the underlying construct or concept it is intended to measure.[33] Typically, it

is evaluated through various methods such as factor analysis, convergent validity and discriminant validity. Almost all studies in this review reported construct validity by measuring the item and total score correlations except for a few validation-only studies that did not perform this type of validity measurement. This suggests variations in the validity of the instruments across different contexts or populations which shall be taken into consideration when used clinically. Criterion-related validity was another type of validity observed in the reviewed studies. One of them was the concurrent validity which was assessed through the correlation between age and total scores of an instrument. Additionally, elevated sensitivity and specificity were also observed in several studies, which indicated the effectiveness of the translated instruments in accurately identifying individuals with and without hearing impairments. These findings underscore the importance of assessing multiple aspects of criterion-related validity to ensure the accuracy and effectiveness of the measurement instruments. Another statistical measure found in the reviewed studies was the test-retest reliability. Majority of studies demonstrated good test-retest reliability, with consistent and stable correlations observed over varying intervals. This indicates that the measurements taken at different points in time were reliable and consistent, suggesting that the instruments maintain their reliability over time. The majority of translation studies plotted normative curves using linear regression analysis, providing valuable reference points for interpreting scores in clinical settings. However, normative curves were less frequently reported in validation-only studies. This suggests that while translation studies focus on establishing normative data for the translated instruments, validation-only studies may prioritize other aspects of reliability and validity of their assessments.

LIMITATIONS

This scoping review was conducted based on the PRISMA statement with a comprehensive literature search strategy. However, several exclusion criteria included during the searches may have inadvertently led to the exclusion of some prominent and relevant research studies. These include the limitation of publication years, the exclusion of non-published literature, publication in a non-English language, and those that could not be retrieved in full article.

CONCLUSION

This current review discovered that all studies performed an extensive evaluation of psychometric properties and feasibility studies to produce an excellent quality of auditory-related behaviour outcome measure for clinical use with the intended population. In summary, the findings from both translation and validation-only studies provide strong support for the reliability and validity of the instruments for assessing listening intervention outcomes. Although some measures were modified to suit the target population, the studies were able to prove consistent reliability and validity outcomes which were comparable with the original measures. However, variations in reporting and the assessment of certain validity aspects across studies highlight the need for standardized methods and transparent reporting practices in future research. This is to ensure the robust and reliable outcome measure instruments in both clinical and research settings. In addition, this review also found a high potential outcome measure, FLI-P, which has strong constructs and practical usability especially for the SLTs who provide learning to listen and spoken language training for children with hearing impairment in Malaysia. It is recommended that future studies attempt to translate and validate some of the reviewed outcome measures into Malaysian main languages (Malay, Mandarin and Tamil) for research and clinical usage.

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CME ARTICLE

Development of ultrasound guided regional anaesthesia in the emergency department, Hospital Kuala Lumpur

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SUMMARY

Ultrasound guided regional anaesthesia is a fast-rising acute pain management modality in emergency departments worldwide. It is a safe and effective alternative to opioid based systemic analgesia. Establishing a standardised and efficient protocol requires a multidisciplinary approach namely involving collaborations between anaesthesiology and emergency medicine counterparts. In this article, we outline our approach in establishing an end-to-end service which is both patient-centred and sustainable.

KEYWORDS:
Ultrasound guided, regional anaesthesia, pain management

INTRODUCTION

Pain management is a part and parcel of every emergency physician's repertoire. Daily treatment of a variety of pain often includes opioids as a pharmacological agent of choice. Even so, several studies revealed that pain management in the emergency setting are often inadequate and delayed.[1]

Ultrasound guided regional anaesthesia (UGRA) is a well-established modality of pain management. In keeping with the nationwide mission for a 'Pain Free Hospital', peripheral nerve block is a safe and reliable alternative. However, most emergency departments have yet to culminate UGRA in their daily practices.[2]

Establishing a Team

UGRA at the emergency department, Hospital Kuala Lumpur was introduced in October 2019. A core team was formed encompassing emergency physicians and medical officers with basic ultrasound proficiency. A total of three emergency physicians and nine medical officers were recruited. Our mission was to provide an alternate modality for pain management. Efforts were made in collaboration with anaesthesiology department, specifically with trained regionalist. According to Stone et. al.[3] a dynamic multidisciplinary teamwork is needed on both local and national scales to avoid delays in the development and implementation of patient-centred, safe procedural care and allow patients the benefits of regional anaesthesia.

Clear objectives of the implementation were first outlined. The primary goal was to provide UGRA as an alternate modality for pain relief, focusing particularly on trauma cases. The aim was to increase pain management effectiveness and reduce the usage of opioid analgesia. Ensuring safety, reliable and efficient UGRA techniques were provided, and an appropriate management pathway was created for post procedural follow up and multidisciplinary collaborations.

Our first order of business was to train the core team members. Our team attended UGRA workshops organised by the anaesthesiology department. It was a two-part training with lectures focusing on introduction to regional anaesthesia, anatomy, sonoanatomy, clinical applications and techniques to perform basic UGRA of the upper limbs, lower limbs and truncal. Part 2 was a hands-on workshop with demonstrations and application of these skills. Upon completion of the training, all members were sent in turn to the operation theatre for a 2-week attachment with our anaesthesiology colleagues. The mainstay of training included nerve visualisation, needle visualisation, ergonomic setting arrangement, anaesthesia agents (dosage and dilution), nerve injury prevention and monitoring. Focus was also placed on managing procedural and drug related complications. This hands-on experience was profound in witnessing and understanding the practical approaches to UGRA and gaining real life experience in performing different types of blocks.

On returning to the emergency department, the team started performing blocks, focusing on trauma patients. All blocks were initially done under supervision of the anaesthesiologist. The overview for all procedures incorporated several crucial elements.

1. Patient selection
2. Consent
3. Preparation
4. Procedure execution
5. Evaluation
6. Monitoring
7. Documentation
8. Database entry and update
9. Follow up

System

The common indications were acute pain management of the extremity, anaesthesia of the extremity for procedures, alternative to procedural sedation and alternative to narcotics in certain patient population (i.e., patients with concomitant mental status change).

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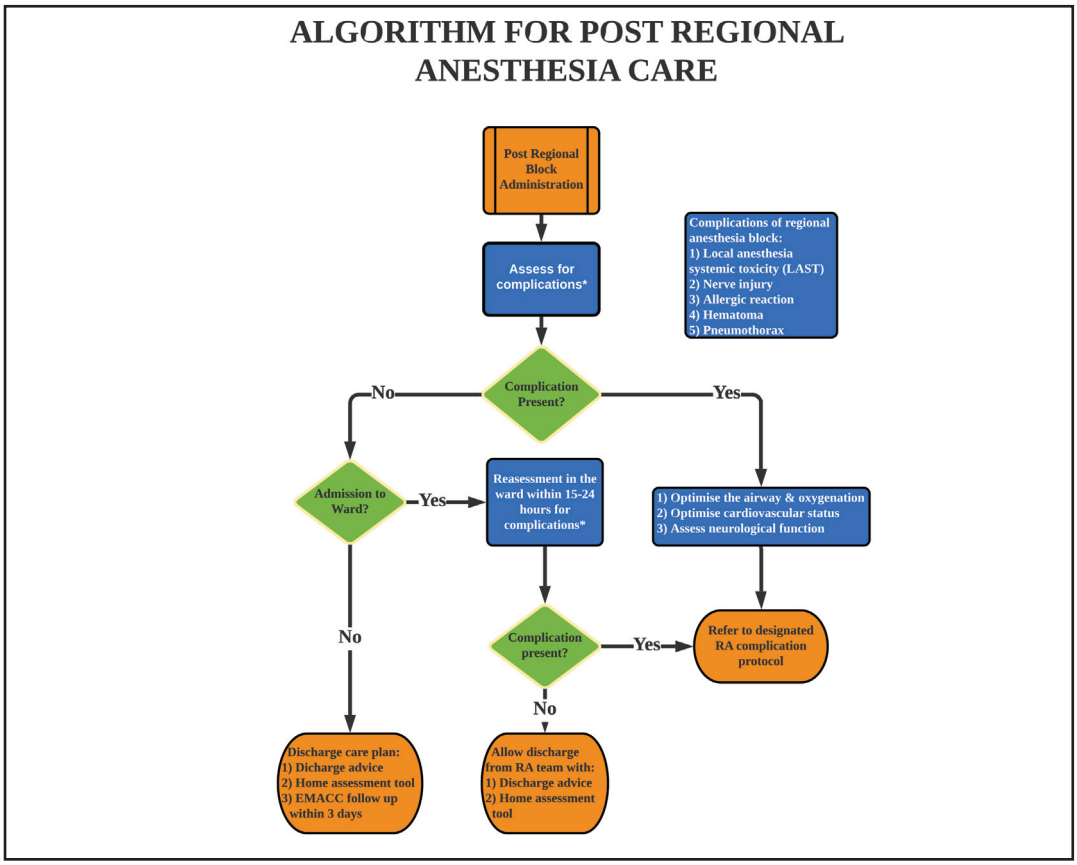

Fig. 1: Algorithm for post regional anaesthesia care.

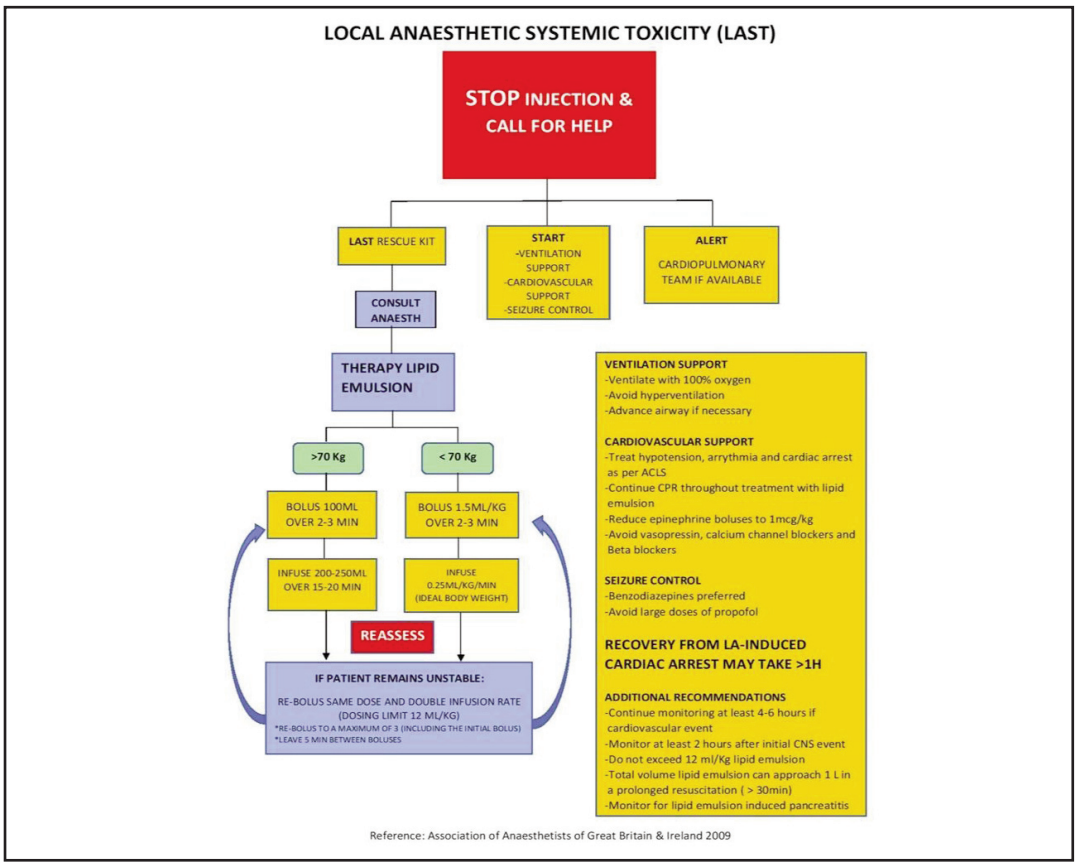

Fig. 2: Local anaesthetics systemic toxicity pathway (LAST).

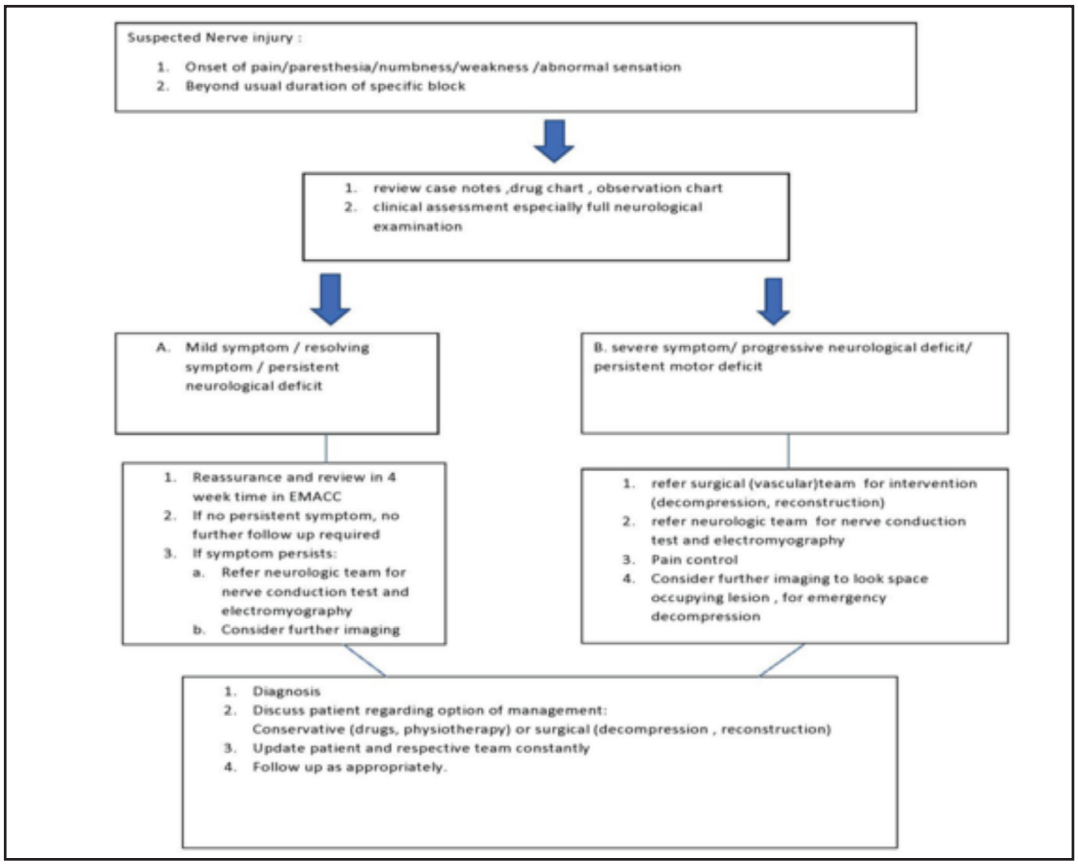

Fig. 3: Nerve injury pathway.

Thus far, these are the common blocks performed:

- Upper limb blocks (44%): supraclavicular, infraclavicular, axillary, interscalene and mid forearm.
- Lower limb blocks (43.2%): femoral, popliteal, fascia iliaca
- Truncal (12.8%): erector spinae plane blocks (ESP), pectoralis and serratus plane nerve blocks (PECS)

Patients with contraindications, such as a history of allergic reaction to local anaesthesia agents, active infection at the injection site, injuries and risk of compartment syndrome, preexisting neurological deficit, extreme obesity obscuring optimal ultrasonographic visualisation and patients on anticoagulant therapy (relative contraindication) were excluded.

We created a customised form with patient and block details and the information was uploaded to the online database. After completion of the blocks the patients were observed for up to 1 hours in the clinical bay. Longer observation periods were imposed on patients with respiratory compromise that underwent brachial plexus blocks. An algorithm for post regional anaesthesia was curated to ensure safe and standardised care. All patients either admitted or discharged were followed up within the next 24 hours for any complications and the general level of pain control was elicited. Follow up is done via teleconference or visits to the respective wards by the team member on duty for the day.

Assessment of pain score pre- and post-procedure overall shows 95% reduction from severe and moderate pain to mild pain, where else the remaining 5% from severe to moderate pain.

Most patient expressed satisfaction post-procedure but a further objective assessment on the satisfaction scale is required.

Structure

To enable a more conducive work environment, we converted a room adjacent to the clinical bay to the regional anaesthesia suite. Here we stored our equipment and database. This area also doubled as our follow up zone as needed.

A tool kit was created encompassing blocking agents and needles to allow us to perform bedside blocks in varies zones. In case the patient cannot be transferred to the regional anaesthesia suite, we performed these blocks in the respective zones instead. This enabled coverage to all zones in the emergency department.

Quality Assurance

All the members underwent predetermined credentialing and privileging prior to performing blocks independently. This was divided into three levels of difficulty. Level 1 incorporated supraclavicular, mid forearm, femoral, popliteal and fascia iliaca block. Level 2 included interscalene, erector spinae

plane (ESP) and PECS block. Finally, Level 3 integrated infraclavicular and axillary blocks. An online logbook was created, and all members were required to comply. For each of this component, observation and assistance of at least five blocks are required, subsequently five blocks are performed under supervision and another five blocks are performed without any supervision and with no complication inquired. Upon completion of the prerequisites, independent performance of the blocks is allowed.

Establishment of regional anaesthesia has sparked a great deal of interest among our peers. We have biannual workshops and annual symposiums for continuous education and targeting recruitment of new members in the emergency fraternity.

Instituting ongoing continuing medical education (CME) and varies training platforms ensures level of competence is maintained among the emergency department staff. It also serves to develop and increase the knowledge and skill among all core team members.

Tackling Complications

All procedures have a risk of complications. Specialised pathways were developed in tackling possible complications such as nerve injury and local anaesthesia toxicity (LAST). LAST rescue kit containing intralipid 20% is kept in the general operating theatre. In a situation whereby it is needed, our anaesthesiology counterparts are consulted and timely administration of the antidote is possible. This is to ensure in the case of any undue outcome, a standardised protocol is in place for the best course of action.

DISCUSSION

Ultrasound guided regional anaesthesia (UGRA) is a promising modality of pain management in the emergency department. Despite its well-established benefits, relatively few emergency departments in Malaysia has fully embraced UGRA in their day-to-day practice. Since bringing UGRA to our emergency department, we find that the vast majority of physicians have embraced this new skill set. All procedures were initially performed under the supervision of the anaesthesiologist in the emergency department, and after the completion of credentialing and privileging, we started performing these procedures independently.

Successful collaboration with our anaesthesiology counterparts has provided a fruitful avenue for continuous education and the development and implementation of patient centred, safe procedural care that allows more patients the access to the benefits of UGRA.[3]

In our experience, bringing UGRA to the emergency department was successful with a well-structured and systematic approach, in collaboration with the anaesthesiology counterparts. Implementation of patient selection criteria, credentialing and privileging, follow up checklist, complication pathways and an online database to monitor our daily procedures, enables a safe, reliable and efficient patient-centred care. One study concluded that despite the many advantages of UGRA such as avoiding the risks of procedural sedation and reduction in the use of opioid analgesia, many emergency medicine trainees do not receive focused education in UGRA, this includes the lack of published curriculum specifically for emergency medicine physicians.[4] In the future, incorporating UGRA in EM training and providing formal certification will empower more emergency physician to confidently and competently include regional anaesthesia in their toolkits.[5]

Ultrasound is readily available in most emergency departments nationwide. Additional training, protocols and increased support from nursing staff are modifiable factors that could facilitate uptake.6 The practical reality is that UGRA is a multimodal analgesia versus a stand-alone ultrasound technique.[2] It is important to have regular hands - on training sessions to ensure we harness our skill set and continuous learning prevails. It will take a collective effort to overcome these barriers before this practice becomes widely adopted in emergency departments across the nation.[7]

Embracing UGRA as part and parcel of pain management in the emergency medicine faculty, adequate training, interdepartmental collaborations and a structured system and protocol is the way forward in providing a pain free experience for our patients.

CONCLUSION

Ultrasound guided regional anaesthesia can be utilised as an integral modality in pain management. A standard protocol clearly highlighting end-to-end care will ensure a safe, patient centred service that can be provided in all emergency departments nationwide.

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