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The Medical Journal of Malaysia

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Acknowledgements:
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Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

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Acknowledgement

The survival outcomes of unilateral retinoblastoma in Malaysia

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ABSTRACT

Retinoblastoma (RB) is the most common malignant intraocular tumour in children and can present as unilateral or bilateral disease. Unilateral RB represents 60% of all cases and tend to present at a relatively advanced stage of RB. Unilateral RB in Malaysia has a one-year survival rate of 99.0% and five-year survival of 93.0%. Shorter lag time, longer duration of follow-up and compliance with follow-up are good prognostic factors for the survival of unilateral RB patients. It is essential to report the prognostic factors associated with unilateral RB in our population. This information will assist healthcare professionals in understanding the factors that influence outcomes and support the development of long-term treatment guideline.

KEYWORDS:
Unilateral, retinoblastoma, survival outcomes, prognostic factors, Malaysia, paediatric

INTRODUCTION

Retinoblastoma (RB) is the most common malignant intraocular tumour in children and can present as unilateral or bilateral disease.[1] Globally, it is estimated to occur in approximately one out of every 16,000-18,000 live births.[2] The incidence of RB in Asia is about 1 in 16,642 live births, and India has the highest incidence of RB, with 1500 new cases per year, accounting for 33.0% of the global burden.[3] Malaysia reports between 27 to 36 cases annually.[4]

Unilateral RB represents 60% of all cases, with a mean age at diagnosis of 24 months.[5] Unilateral cases tend to present at a relatively advanced stage of RB, when compared with bilateral cases.[6] The reported mean ocular survival time is 20.67 months, and the overall survival rate is 96%. Initial chemotherapy, along with enucleation, is reported to reduce mortality in cases of advanced unilateral disease.[5,7]

There are limited data on the incidence, survival rates and prognostic factors for unilateral RB in Southeast Asia, including Malaysia. Identification of previously unreported evidence-based prognostic factors for survival of unilateral RB and its survival rate specific to our population will help to educate healthcare professionals and the community regarding the importance of recognising factors affecting the survival of unilateral RB and facilitating the development of integrated long-term clinical management guidelines for RB survivors.

Survival of unilateral retinoblastoma in Malaysia

The Malaysian National Eye Database's Retinoblastoma Registry has a collection of data on RB cases throughout Malaysia in all main tertiary hospitals with paediatric ophthalmology services. Analysing data of 114 patients from 2001 to 2020 that met the criteria of being diagnosed with unilateral RB with the age of less than 17 years old, 65 (57%) were from Hospital Kuala Lumpur, 27 (24%) were from Hospital Pakar Universiti Sains Malaysia and 22 (19%) were from Hospital Wanita Kanak-Kanak Sabah (Table I).

The mean age at diagnosis was 29 (18.9) months. This is a slightly younger age group, compared to unilateral RB patients in a Pakistani study, which was 37 months, and older than patients in the United States (US), which was 25 months.[8,9] The mean age at diagnosis in Malaysian children is similar to that from other South East Asian countries, as the mean age at diagnosis in the Philippines ranged from 24-33 months, with a significantly older age at presentation in unilateral disease, which was attributed to financial constraints and misdiagnoses.[10,11] Malaysian children showed fairly similar involvement in both genders in unilateral RB; boys accounted for 57.0% of cases, and girls made up the remaining 43.0%.

The white reflex (90.4%) was the most common first symptom of disease parents noticed, followed by strabismus (22.8%). This is consistent with the global RB presentation reported by Fabian et al.[12] Leukocoria (96.5%) was the most common sign observed in Malaysian children and is consistent with global data. Proptosis, which represents advanced disease, is reported to be higher in other Asian countries, such as Pakistan (22.0%) and Indonesia (66.0%).[13,14] Most (57.1%) of the non-surviving patients presented with proptosis, and all non-surviving patients were extraocular and diagnosed with International Retinoblastoma Staging System stage IV disease at presentation. This is the most advanced stage of disease and is linked to high mortality and a grave prognosis.[15] This stage

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Table I: Demographic and clinical data of Malaysian children with unilateral retinoblastoma

Variables	Frequency, n (%)		
	Death (n=7)	Censored (n=107)	Total (N=114)
Age at diagnosis (months)			
Less than 24 months	2 (28.6)	18 (16.8)	20 (17.5)
24 - 48 months	3 (42.9)	31 (29.0)	34 (29.8)
More than 48 months	2 (28.6)	58 (54.2)	60 (52.6)
Mean (SD)	23 (16.9)	29 (19.1)	29 (18.9)
Range	6 - 48	2 - 106	2 - 106
Gender			
Male	4 (57.1)	61 (57.0)	65 (57.0)
Female	3 (42.9)	46 (43.0)	49 (43.0)
Race			
Malay	6 (85.7)	70 (65.4)	76 (66.7)
Chinese	0	10 (9.3)	10 (8.8)
Indian	0	6 (5.6)	6 (5.3)
Others	1 (14.3)	21 (19.6)	22 (19.3)
Lag time			
Less than 6 months	1 (14.3)	79 (73.8)	80 (70.2)
More than 6 months	6 (85.7)	28 (26.2)	34 (29.8)
Mean (SD)	12 (11.0)	6 (10.7)	6 (10.8)
Range	2 - 36	0 - 96	0 - 96
Clinical features			
Leukocoria	7 (100.0)	103 (96.3)	110 (96.5)
Retinal detachment	3 (42.9)	31 (29.0)	34 (29.8)
Secondary glaucoma	3 (42.9)	17 (15.9)	20 (17.5)
Proptosis	4 (57.1)	9 (8.4)	13 (11.4)
Strabismus	0	11 (10.3)	11 (9.6)
Tumour extension			
Intraocular	0	98 (91.6)	98 (86.0)
Extraocular	7 (100.0)	9 (8.4)	16 (14.0)
Staging			
Intraocular A - B	0	2 (1.9)	2 (1.8)
Intraocular C - D	0	31 (29.0)	31 (27.2)
Intraocular E	0	65 (60.7)	65 (57.0)
Extraocular 0 - II	0	3 (2.8)	3 (2.6)
Extraocular III	0	1 (0.9)	1 (0.9)
Extraocular IV	7 (100.0)	5 (4.7)	12 (10.5)
Second neoplasm	1 (14.3)	0	1 (0.9)
Treatment received			
Enucleation	4 (57.1)	102 (95.3)	106 (93.0)
Chemotherapy	7 (100.0)	63 (58.9)	70 (61.4)
Focal therapy	0	8 (7.5)	8 (7.0)
EBRT	0	4 (3.7)	4 (3.5)
Non-compliance to follow-up			
Yes	5 (71.4)	10 (9.3)	15 (13.2)
No	2 (28.6)	97 (90.7)	99 (86.8)
Age at death (months)			
Mean (SD)	56 (26.2)	NA	NA
Range	23 - 97	NA	NA
Cause of death			
Disease progression	4 (3.5)	NA	NA
Severe sepsis	3 (2.6)	NA	NA

Abbreviations: EBRT, external beam radiotherapy; NA, not applicable. Censored : survived patients beyond the end of study period

of disease is seen at a high frequency in developing countries.[12] Similarly, Jain et al. reported that most of their study's non-surviving patients had advanced disease at presentation; 58.8-92.3% had extraocular disease.[16]

The hereditary form of unilateral RB, which were based on clinical assumption were present in only two patients, who were sisters. The low incidence of the hereditary form is likely because the incidence of the hereditary form is higher in bilateral cases.[17] Hereditary RB also includes a higher risk of developing a second primary neoplasm, which is 20% in those who have not received radiotherapy and 40-50% of those who have been irradiated.[18] However, data from the Malaysian National Eye Database's Retinoblastoma Registry showed only one (0.9%) patient who developed second neoplasm, and it was a paraganglioma. This patient had a sporadic form of RB and received systemic chemotherapy without any radiotherapy.

Enucleation (93.0%) and systemic chemotherapy (70.0%) were the most common treatment modalities given (Table II). This is because the majority of cases were diagnosed with International Classification for Retinoblastoma group E disease (57.0%), which warrants treatment with systemic

Table II: Treatment modalities received by Malaysian children with unilateral retinoblastoma

Variables	Frequency, n (%)			
	Enucleation	Chemotherapy	EBRT	Focal Therapy
Tumour extension				
Intraocular (n=98)	93 (94.9)	54 (55.1)	2 (2.0)	8 (8.2)
Extraocular (n=16)	13 (81.3)	16 (100.0)	2 (12.5)	0
Staging				
Intraocular A - B (n=2)	1 (50.0)	1 (50.0)	0	0
Intraocular C - D (n=31)	28 (90.3)	12 (38.7)	0	8 (25.8)
Intraocular E (n=65)	64 (98.5)	41 (63.1)	2 (3.1)	0
Extraocular 0 - II (n=3)	3 (100.0)	3 (100.0)	1 (33.3)	0
Extraocular III (n=1)	1 (100.0)	1 (100.0)	0	0
Extraocular IV (n=12)	9 (75.0)	12 (100.0)	1 (8.3)	0

Abbreviations: EBRT, external beam radiotherapy.

Table III: Overall unilateral retinoblastoma survival in Malaysia

	1-year survival		3-year survival		5-year survival	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Unilateral retinoblastoma	113 (99)	97,100	111 (97)	94,100	107 (93)	88,98

Abbreviations: CI; Confidence interval.

Table IV: The associated prognostic factors for survival of children with unilateral retinoblastoma in Malaysia

Variables	Crude HR	(95% CI)	p-Value[a]	Adjusted HR	(95% CI)	p-Value[b]
Age at diagnosis (months)						
Less than 24 months	-	-				
24 - 48 months	0.81	0.14, 4.87	0.82			
More than 48 months	0.31	0.04, 2.20	0.24			
Gender						
Male	-	-				
Female	0.98	0.22, 4.38	0.98			
Lag time						
Less than 6 months	-	-				
More than 6 months	14.26	1.71,118.48	0.014	102.04	1.58,6583.95	0.030
Enucleation						
Yes	-	-				
No	0.08	0.02,0.36	0.001	0.04	0.01,1.08	0.055
Duration of follow up	0.90	0.86,0.95	0.000	0.02	0.89,0.99	0.026
History of default						
Yes	0.05	0.01, 0.27	0.000	0.03	0.01,0.86	0.041
No	-	-				

[a]simple Cox Hazard Regression, [b]multiple Cox Hazard Regression
Abbreviations: HR; hazard ratio, CI; confidence interval, p<0.05 significant

Table V: Summary of literature of factors affecting survival rate of children with retinoblastoma in Asia

Country	Author / Year	Older age at	on-compliance diagnosis	Extraocular to follow-up	Lag time extension	Duration of follow-up
India	Chaw et al. / 2016	✓	NA	✓	✓	NA
Thailand	Rojanaporn et al. / 2020	✓	NA	✓	✓	NA
Singapore	Aung et al. / 2009	✓	NA	NA	✓	NA
Taiwan	Chang et al. / 2006	X	NA	✓	✓	NA
Korea	Kim et al. / 2020	X	NA	NA	NA	NA
Malaysia	Our study / 2025	X	✓	X	✓	✓

✓; Significant factors with 95% Confidence Interval or p < 0.05. X; not significant, NA; not available.

chemotherapy and enucleation.[19] Chemotherapy in intraocular disease were given to reduce tumour size and reduce risk of metastases. Focal therapy (7.0%) was not given as often, as it is recommended for earlier stages of disease, which had lower incidence levels in Malaysian children. External beam radiotherapy (3.5%) was the least treatment modality given as it is usually reserved for cases not responding well to chemotherapy. Another reason for the lack of these treatment modalities could be because these treatments are not available in most tertiary centres in Malaysia. In a study conducted in Egypt, enucleation (53.7%) was the main treatment given, followed by chemotherapy (46.3%), and most of their cases were groups D (41.9%) and E (33.5%).[5] Globally, enucleation remains an important treatment option, despite advancements in globe-salvage therapy.[12]

The overall survival rates of Malaysian children with unilateral RB were 99.0% (after one year), 97.0% (after three years) and 93.0% (after five years) as shown in Table III. This is slightly lower than the five-year survival rates for unilateral RB in Great Britain (97.0%) and China (95.5%).[20,21] A country's income level (low vs. high) has been reported as a risk factor of poor survival.[12] This is because patients in lower income countries presented with more aggressive disease, and these countries often lack sophisticated treatment and investigation facilities such as MRI, radiotherapy and focal treatments. This leads to limited disease management options. Better survival was attributed to the earlier diagnosis and treatment common in higher income countries, which is consistent with shorter lag time as a significant good prognostic factor in our data.

There are limited data on the survival rates specific to unilateral RB in other countries. The reported one-, three- and five-year survival rates of RB in India are 83.0-94.0%, 73.0-91.0% and 68.0-90.0%, respectively.[22,23] Survival rates in other Asian countries, such as Taiwan, Nepal, Indonesia and Thailand, are 64.4%, 26.6%, 20.0% and 73.0%, respectively.[24-27] The poor survival rate in Indonesia is attributed to high rates of treatment refusal (16.0%), treatment abandonment (40.0%) and a preference for less expensive alternative medicine.[24] In Malaysia, 2.6% of the patients refused treatment, but there were no patients who abandoned treatment once treatment commenced. Among these patients, 15 (13.2%) had a history of default prior to starting treatment, but they were compliant throughout the course of treatment.

Lag time less than six months, longer duration of follow-up and compliance with follow-up were the significant good prognostic factors in Malaysian children with unilateral RB, based on a multivariate analysis (Table IV). Shorter lag time has also been reported as a significant prognostic factor in India, Thailand and Singapore.[22,28,29] A global RB study also reported that early detection is the most important prerequisite for a better outcome.[1] Here, longer lag times were due to the lack of awareness by parents, parents' dilemma, parents' preferences for alternative medicine, financial constraints and a refusal to seek an earlier medical consultation. Roland et al. reported that the cause of delay in South Asian countries is also attributable to a lack of knowledge on the severity of the disease, a lack of access to healthcare and resorting to alternative medicine.[15]

Limited data are available on the impact of follow-up duration and compliance as prognostic factors for the survival of unilateral RB patients. Fabian et al. reported that higher income countries with better survival rates had a longer follow-up time, of 37 months, compared to low-income countries (14.7 months).[12] A longer duration of follow-up allows managing doctors to identify patients who develop complications or respond poorly to treatment. Therefore, necessary interventions to avoid further complications could be administered, hence preventing unwanted complications and ensuring better survival. The reason for defaulting on follow-up after a diagnosis in Malaysia was due to poor insight on the severity of the disease and resorting to alternative medicine, as in other South Asian countries.[15] Those who defaulted ultimately presented again to managing institutions, once the disease had progressed and parents realised that alternative medicine had no effect on their children.

Extraocular extension was an insignificant prognostic factor, although studies in India and Thailand reported that rates of extraocular extension were significant.[22,28] More than half (56.0%) of Malaysian patients with extraocular extension survived, and a majority of them had shorter lag times (56.3%) with good compliance with follow-up (66.7%). By contrast, a majority of the non-surviving patients had longer lag times (85.7%) and were non-compliant with follow-up (71.4%). Therefore, even if patients had extraocular extension at presentation, a shorter lag time and compliance with follow-up led to better survival outcomes for these patients ($p < 0.05$). This is because they were able to receive appropriate and adequate treatment as early as possible, compared to patients who experienced a delay in beginning treatment. Although the non-surviving patients did receive treatment, the progression of disease and complications of severe sepsis affected the efficacy and adequacy of treatment, hence their poor outcomes.

An older age at diagnosis was not identified as a significant prognostic factor in our data, despite previously reported studies claiming that age at diagnosis was significant.25,28-30 Among the survivors, 54.2% had an older age at diagnosis (48 months), compared to the non-surviving patients (23 months). In short, early onset RB does not indicate a poor survival prognosis in Malaysian children with unilateral RB. Similarly, studies in Taiwan and Korean did not find age at diagnosis to be a significant prognostic factor.[31,32] Table V summarises the factors affecting the survival rate in Asia.

CONCLUSION

The outcomes of this study highlight an urgent need to improve RB awareness among parents, healthcare workers and the community for earlier detection, better access to treatment and ensuring compliance with follow-up. The survival rate of unilateral RB in Malaysia can be improved to make it a zero-death cancer, but prognostic factors for survival must be managed promptly to ensure better survival. A national-level initiative should be proposed to achieve this goal which includes continuous education on RB awareness for primary healthcare providers, parents and the community.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Cross-cultural adaptation and validation of the Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM)

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ABSTRACT

Introduction: Cirrhosis is common in Malaysia, but no questionnaire in the local language (Malay) has been developed to assess patients' knowledge of this disease. This study aimed to adapt and validate the Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM).

Materials and Methods: ASK-QM was translated from English to Malay according to international guidelines. It was validated among cirrhotic patient who understand Malay language from two major liver centers in Klang Valley, Malaysia (University of Malaya and Hospital Selayang) from January 2021 to March 2022, at week 0 and 2. Patients with hepatic encephalopathy were excluded.

Results: 121 out of 132 patients with cirrhosis agreed to participate (response rate=91.7%). The overall median score of the ASK-QM was 54.5 [38.6-68.2] and the difficulty factor was 0.5 (range: 0.1-0.8 for each domain). Confirmatory factor analysis showed a good model fit with results of Comparative fit index (CFI) ranging from 0.836 to 1.000, whilst, the Tucker–Lewis index (TLI) ranged from 0.690 to 1.004 across all four domains. The root mean square error of approximation (RMSEA) value was reported from 0.000 to 0.100. For standardized root mean squared residual (SRMR) was from 0.008 to 0.015. Patients with tertiary education scored higher compared to those without (63.6 [45.5-77.3] vs 52.3 [36.4-63.6], p<0.05). The overall Kuder-Richardson (KR) coefficient was 0.761 indicating adequate internal consistency. Test-retest among 82 out of 121 patients (response rate=67.7%) demonstrated adequate reliability with eighteen out of 22 items having Wilcoxon signed-rank test values that were statistically not significant, p>0.005.

Conclusion: The ASK-QM was found to be a valid and reliable questionnaire for evaluating knowledge of liver cirrhosis amongst Malay-speaking adults.

KEYWORDS:
Cirrhosis, knowledge, questionnaire, adaptation, translation, validation study

INTRODUCTION

Liver cirrhosis is a condition of disruption of the liver parenchymal as a result of necrosis, regeneration, and diffuse fibrosis.[1] In 2019, liver cirrhosis was the 11th most common cause of death worldwide.[2] According to Global Burden of Disease, viral hepatitis B has been recognised as the main cause of chronic liver disease, including cirrhosis for the past 30 years.[3] This trend could be observed in Malaysia as well, where viral hepatitis B is still the main cause of liver cirrhosis, acute hepatitis-related death, and hepatocellular carcinoma.[4,5]

Knowledge about cirrhosis plays an important role in managing cirrhotic patients effectively.[6] However, most studies showed that patients' knowledge about liver cirrhosis was still low.[6-8] Goldsworthy et al. reported that only 10% of cirrhotic patients were aware of the reason for the need for routine liver ultrasound and oesophageagastroscopy.[7] Lack of patient knowledge regarding liver cirrhosis impacts a physician's clinical management, which may then leads to an increase in morbidity due to poor medication adherence and frequent re-hospitalizations.[9-11] An Australian study showed that many adults with viral hepatitis B were unaware of the risk of cirrhosis and hepatocellular carcinoma.[12] Patients with lower health literacy had significantly higher median Model for End-Stage Liver Disease (MELD) scores, which was linked to higher mortality and poorer outcomes.[13] In Malaysia, people who were older and had a lower education level or household income had a lower level of health literacy.[14]

To date, several questionnaires have been developed worldwide to evaluate patients' knowledge of liver cirrhosis.[6,7,15,16] However, many of these questionnaires only assessed knowledge regarding clinical management and disease outcomes.[6,7,15,16] Hence, we developed and validated the Adult cirrhosiS Knowledge Questionnaire (ASK-Q) in English, which consisted of four domains: 1)self-understanding (5 items), 2)aetiology (5 items), 3)complication (4 items), and 4)management of liver cirrhosis (8 items).[17] The Kuder-Richardson coefficient was 0.760 indicated that the ASK-Q had good validity and reliability.[17] However, Malay is the national language of Malaysia, spoken by a most of its citizens, and spoken by the Austronesian family in Brunei. To date, not many questionnaires that assess the knowledge of liver cirrhosis exist in Malay. Hence, we aimed to cross-culturally adapt and validate the Malay version of ASK-Q to ensure it is both linguistically and culturally relevant for Malay-speaking

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populations, so that this questionnaire can be administered to a wider population around the Malay Archipelago.

MATERIALS AND METHODS

Cross-cultural adaptation of the Adult cirrhosiS Knowledge Questionnaire (ASK-Q) from English to Malay (ASK-QM)

The original English version of the ASK-Q which was developed and validated by our team, has been published and widely utilised in cirrhotic patient.[17] We have undertaken the task to translate into Malay language according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guideline.[18] The production of a Malay version of ASK-Q followed a rigorous process involving forward and backward translation to ensure conceptual and cultural equivalence. The forward translation from English to Malay was conducted independently by a medical and non-medical translator. The expert panel (consisting of four gastroenterologists/hepatologists and an academician with experience in the development and validation of questionnaires) reviewed and integrated the translations into a preliminary Malay version of ASK-Q. Similarly, backward translation from Malay to English was performed by another pair of medical and non-medical translators. Subsequently, a discussion of the expert panel, it resulted in a single culturally adapted Malay version of ASK-Q. The final version of the ASK-QM was pilot-tested among five Malay native-speaking participants (60% men; 40% women) who were diagnosed with liver cirrhosis were asked to answer the ASK-QM. The aim was to assess the clarity, relevance, and content understanding of the ASK-QM. All participants completed the questionnaire without difficulty and mentioned that the statements were clear, easy to understand and culturally appropriate. The average time taken to complete the questionnaire was approximately eight minutes. Hence, no modifications were made and version 4 of the ASK-QM was used as the final questionnaire (Figure 1).

Validation of the Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM)

The ASK-QM was then validated at two tertiary hospitals in Malaysia: University of Malaya Medical Centre, Kuala Lumpur, and Hospital Selayang, Selangor from January 2021 to March 2022. Patients who had liver cirrhosis with or without decompensation, aged ≥18 years old, who could understand Malay were recruited from the hepatology clinics, endoscopy rooms, or wards. Liver cirrhosis was diagnosed by imaging (ultrasonography or computed tomography scan), histopathology, or transient elastography (Fibroscan®). Causes of liver cirrhosis include chronic viral hepatitis (hepatitis B and C), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, methotrexate-related liver fibrosis, and cryptogenic liver cirrhosis. Sample size was calculated based on the recommended ratio of 5 participants to each item in the questionnaire, to perform factor analysis.[19] Since the ASK-QM has 22 items, the sample size required was 110 patients.

Patient characteristics

A baseline demographic form was used to collect patient demographic details such as age, gender, ethnicity, duration of diagnosis, aetiology of liver cirrhosis, educational background, and severity of liver cirrhosis (using the Child-Pugh score).[20]

Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM)

The ASK-QM consists of four domains: self-understanding (5 items), aetiology (5 items), complications (4 items), and management of cirrhosis (8 items) with a total of 22 items. Each item had three options (yes, no and don't know). A correct response was awarded one point while 0 points was allocated for incorrect and "don't know" responses. The total score of each domain was calculated and converted to percentages (%). A higher score indicated higher knowledge of liver cirrhosis.

Procedure

Patients were recruited via convenience sampling. The purpose of the study was explained to patients using a participant information sheet. For those who agreed to participate, written informed consent was obtained. Patients were asked to fill the baseline demographic form and the ASK-QM at baseline. Two weeks later, the researcher contacted each patient via phone for a retest of the ASK-QM.

Ethical approval

The study was approved by the Medical Research Ethics Committee of the University Malaya Medical Centre (MREC ID NO: 2020827-9020) and National Medical Research Register (MERC ID NO: NMRR-20-3295-56800)

Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26 Armonk, NY: IBM Corp.) and SPSS AMOS version 23 (Armonk, NY: IBM Corp.). Since data were not normally distributed, non-parametric tests were used. Categorical variables were expressed as frequencies with percentages (%), whilst continuous data were presented as median with inter-quartile range. Non-parametric tests were used to analyse the data. Statistical significance was assumed at a p-value of <0.05.

Construct validity

The difficulty factor of the ASK-QM was calculated using the number of patients who answered the item correctly, divided by the total number of patients: 0.8-1.0 was classified as too easy, 0.3-0.8 as moderate, and ≤ 0.3 as too hard.21 An ideal questionnaire should have a difficulty factor ranging from 0.3 to 0.7.[21]

Confirmatory factor analysis (CFA) was conducted to assess the factor structure of ASK-QM. There are various criteria for the model of fit indices. Comparative fit index (CFI) ranges from 0 to 1. The cut-off point of good fit is 0.9, while > 0.95 indicates a perfect fit.[22] Tucker–Lewis index (TLI) values with > 0.90 could ruminate as a good fit, 0.80-0.90 a marginal fit, and <0.80 a poor fit.[23] For standardized root mean squared residual (SRMR) values: <0.08 is generally considered a good model fit.[24] The root mean square error of approximation (RMSEA) values of <0.05 are good, 0.05 to 0.08 are considered acceptable, and marginal results from 0.081 to 0.10, and $>$ 0.1 is considered poor.[25]

Table I: Demographic and clinical characteristics of patients

Characteristic	n=121 (%)
Gender	
Male	72 (59.5)
Female	49 (40.5)
Median age in years, (IQR)	62.0, (55.5-69.0)
Ethnicity	
Malay	58 (47.9)
Chinese	41 (33.9)
Indian	18 (14.9)
Others*	4 (3.3)
Education level	
Primary	39 (32.2)
Secondary	55 (45.5)
Tertiary	27 (22.3)
Aetiology of liver cirrhosis **	
Viral hepatitis B	45 (35.2)
Viral hepatitis C	27 (21.1)
Non-alcoholic fatty liver disease	25 (19.5)
Alcoholic liver disease	13 (10.2)
Autoimmune hepatitis	8 (6.3)
Cryptogenic liver disease	5 (3.9)
Primary biliary cholangitis	4 (3.1)
Graft cirrhosis	1 (0.8)
Child-Pugh Class (Child-Pugh score)	
A (5-6)	65 (53.7)
B (7-9)	37 (30.6)
C (10-15)	19 (15.7)

- * Filipino – 2 ; Indonesian – 2
- ** Some patients had more than 1 aetiology of liver cirrhosis.

Discriminative validity assesses if the questionnaire is able to discriminate between two distinct groups.[26] We hypothesized that patients with tertiary education would have higher knowledge scores compared to those patients without. Chi-square tests were used for individual items in each domain, while the Mann-Whitney U-test was used for continuous data (domain scores and total test scores).

Reliability

Reliability was assessed by evaluating the internal consistency of the ASK-QM. The response options in the ASK-QM was dichotomous (meaning that patients either answered the items correctly or incorrectly). Hence, Kuder-Richardson was used to calculate internal consistency.26,27 Kuder-Richardson values are classified as follows: ≥0.80- high internal reliability, ≥ 0.51-0.79- adequate internal reliability, ≤0.50- unacceptable internal reliability.[27]

Kappa was used to assess the reliability of the ASK-QM at test-retest for individual items, whilst the Wilcoxon signed ranked test was used for continuous data (domain scores and total test scores).[28] Kappa values can be classified as follows: >0.80 as a very good agreement; 0.61-0.80 as good agreement; 0.41-0.60 as moderate agreement; 0.21-0.4 as fair agreement and below as poor agreement.[29]

RESULTS

A total of 121 out of 132 patients with liver cirrhosis agreed to participate in the study (response rate = 91.7%). Majority were male (59.5%), completed secondary education (45.4%), and had a median age of 62 years. The main aetiology of liver cirrhosis was viral hepatitis B (35.2%), followed by viral hepatitis C (21.1%) and non-alcoholic fatty liver disease (19.5%), with Child-Pugh class A (53.7%) scores (Table I).

Confirmatory factor analysis

CFA revealed that the CFI ranged from 0.836 to 1.000, whilst, the TLI ranged from 0.690 to 1.004 across all four domains. The RMSEA value was reported from 0.000 to 0.100. SRMR was from 0.008 to 0.015. CFI showed an adequate fit in the domains A (Self-understanding), B (Aetiologies), and D (Management) with a value of 0.845, 0.836, and 0.857 respectively. TLI showed mediocre fit in domains A, B, and D with values of 0.690, 0.671, and 0.799 correspondingly. Domain C (Complication) indicated a perfect fit for CFI (1.000) and TLI (1.004). Generally, SRMR indicated a good fit though across all domains (values of 0.015, 0.012, 0.008, and 0.014). RMSEA showed acceptable fit in domains A, C, and D (0.080, 0.000, and 0.042). Domain B indicated a poor fit with an RMSEA value of 0.100.

Validity

The overall difficulty factor of the ASK-QM was 0.5 (range: 0.1 to 0.8). A total of 9/22 (40.9%) items were "easy" (score≥0.7) 11 out of 22(50.0%) items were "moderately easy" (scored between 0.3-0.7) and 2 out of 22(9.1%) items were "difficult" (score of <0.3). The overall total median score was 54.5 [38.6-68.2]. Patients had the highest median score in the domain of "self-understanding" (60.0 [40.0-80.0]), followed by "aetiology" (60.0 [40.0-80.0]), "complications" (50.0 [25.0-75.0]) and "management of cirrhosis" (50.0 [25.0-62.5]).

Table II: Discriminative validity of the Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM)

Domain	Items	Difficulty factor (n=121)	Total knowledge score (n=121) Median [IQR]	Tertiary education (n= 27)			Secondary education and below (n=94)			Chi2 Test/ Mann-Whitney U-test
				Mean ± SD	Median [IQR]	No. of Correct responses [n (%)]	Mean ± SD	Median [IQR]	No. of Correct responses [n (%)]	p-value
Self-understanding of liver cirrhosis	A1	0.4		0.5 ± 0.5	1.0	15 (55.6)	0.4 ± 0.5	0.0	38 (40.4)	0.163
	A2	0.5		0.6 ± 0.5	1.0	15 (55.6)	0.5 ± 0.5	0.0	49 (52.1)	0.753
	A3	0.7		0.7 ± 0.5	1.0	18 (66.7)	0.7 ± 0.5	1.0	68 (72.3)	0.567
	A4	0.7		0.6 ± 0.5	1.0	15 (55.6)	0.7 ± 0.5	1.0	68 (72.3)	0.098
	A5	0.5		0.7 ± 0.5	1.0	19 (70.4)	0.5 ± 0.5	0.0	45 (47.9)	0.038*
	Domain score (%)	0.6	60.0 [40.0-80.0]	60.8 ± 32.1	60.0 [40.0-80.0]		57.0 ± 26.1	60.0 [40.0-80.0]		0.371
Aetiologies of liver cirrhosis	B1	0.7		0.7 ± 0.4	1.0	20 (74.1)	0.7 ± 0.4	1.0	69 (73.4)	0.945
	B2	0.7		0.7 ± 0.4	1.0	20 (74.1)	0.7 ± 0.5	1.0	64 (68.1)	0.552
	B3	0.8		0.8 ± 0.4	1.0	22 (81.5)	0.7 ± 0.4	1.0	70 (74.5)	0.452
	B4	0.4		0.4 ± 0.5	0.0	12 (44.4)	0.4 ± 0.5	0.0	37 (39.4)	0.635
	B5	0.3		0.3 ± 0.5	0.0	9 (33.3)	0.3 ± 0.5	0.0	27 (28.7)	0.644
	Domain score (%)	0.6	60.0 [40.0-80.0]	61.4 ± 29.8	60.0 [40.0-80.0]		56.8 ± 26.2	60.0 [40.0-80.0]		0.277
Complications of liver cirrhosis	C1	0.7		0.8 ± 0.4	1.0	22 (81.5)	0.7 ± 0.5	1.0	61 (64.9)	0.102
	C2	0.6		0.8 ± 0.4	1.0	21 (77.8)	0.6 ± 0.5	1.0	53 (56.4)	0.044*
	C3	0.3		0.4 ± 0.5	0.0	10 (37.0)	0.3 ± 0.5	0.0	31 (33.0)	0.695
	C4	0.7		0.7 ± 0.5	1.0	18 (66.7)	0.7 ± 0.5	1.0	61 (64.9)	0.865
	Domain score (%)	0.5	50.0 [25.0-75.0]	65.8 ± 27.9	75.0 [50.0-87.5]		54.8 ± 32.7	50.0 [25.0-75.0]		0.119
Management of liver cirrhosis	D1	0.1		0.2 ± 0.4	0.0	4 (14.8)	0.1 ± 0.2	0.0	3 (3.2)	0.023*
	D2	0.5		0.7 ± 0.5	1.0	18 (66.7)	0.5 ± 0.5	0.0	46 (48.9)	0.104
	D3	0.6		0.7 ± 0.5	1.0	19 (70.4)	0.6 ± 0.5	1.0	57 (60.6)	0.356
	D4	0.7		0.9 ± 0.4	1.0	23 (85.2)	0.7 ± 0.5	1.0	67 (71.3)	0.145
	D5	0.3		0.3 ± 0.5	0.0	9 (33.3)	0.3 ± 0.5	0.0	26 (28.0)	0.588
	D6	0.4		0.6 ± 0.5	1.0	16 (59.3)	0.4 ± 0.5	0.0	34 (36.2)	0.032*
	D7	0.7		0.7 ± 0.4	1.0	20 (74.1)	0.7 ± 0.5	1.0	64 (68.1)	0.552
	D8	0.2		0.2 ± 0.4	0.0	6 (22.2)	0.2 ± 0.4	0.0	13 (13.8)	0.291
	Domain score (%)	0.4	50.0 [37.5-62.5]	53.2 ± 19.5	50.0 [37.5-75.0]		41.4 ± 17.6	37.5 [25.0-50.0]		0.006*
	Total Domain (%)	0.5	54.5 [38.6-68.2]	59.1 ± 21.9	63.6 [45.5-77.3]		50.9 ± 17.9	52.3 [36.4-63.6]		0.034*

• Note: #Chi2 test was used for categorical variables while the Mann-Whitney U-test was used for continuous variables; *statistically significant at p<0.05.

Table III: Reliability of the Malay Adult cirrhosiS Knowledge Questionnaire (ASK-QM)

Domain	Items	Kuder-Richardson	Corrected item knowledge Total Correlation	Kuder-Richardson if Item deleted	Test (N=121)			Retest (N=82)			Kappa measurement of agreement value	Wilcoxon signed-ranked test p value
					Mean ± SD	Median	No. of Correct responses [n (%)]	Mean ± SD	Median	No. of Correct responses [n (%)]		
Self-understanding of liver cirrhosis	A1	0.509	0.326	0.358	0.4± 0.5	0.0	53 (43.8)	0.4± 0.5	0.0	33 (40.2)	0.632	0.118
	A2		0.255	0.409	0.5± 0.5	1.0	64 (52.9)	0.6± 0.5	1.0	49 (59.8)	0.431	0.082
	A3		0.270	0.400	0.7± 0.5							
	1.0	86 (71.1)	0.7± 0.4	1.0	60 (73.2)	0.434	0.648					
	A4		0.240	0.420	0.7± 0.5	1.0	83 (68.6)	0.6± 0.5	1.0	48 (58.5)	0.168	0.216
	A5		0.163	0.474	0.5± 0.5	1.0	64 (52.9)	0.5± 0.5	0.0	39 (47.6)	0.245	0.719
Aetiologies of liver cirrhosis	B1	0.534	0.240	0.513	0.7± 0.5	1.0	89 (73.6)	0.7± 0.4	1.0	61 (74.4)	0.537	0.791
	B2		0.289	0.485	0.7± 0.4	1.0	84 (69.4)	0.7± 0.5	1.0	54 (65.9)	0.408	0.819
	B3		0.355	0.447	0.8± 0.4	1.0	92 (76.0)	0.6± 0.5	1.0	51 (62.2)	0.237	0.021*
	B4		0.356	0.441	0.4± 0.5	0.0	49 (40.5)	0.4± 0.5	0.0	34 (41.5)	0.268	0.853
	B5		0.260	0.502	0.3± 0.5	0.0	36 (29.8)	0.4± 0.5	0.0	34 (41.5)	0.288	0.054
Complications of liver cirrhosis	C1	0.585	0.426	0.467	0.7± 0.5	1.0	83 (68.6)	0.7± 0.5	1.0	59 (72.0)	0.456	1.000
	C2		0.494	0.405	0.6± 0.5	1.0	74 (61.2)	0.5± 0.5	1.0	42 (51.2)	0.192	0.486
	C3		0.360	0.519	0.3± 0.5	0.0	41 (33.9)	0.5± 0.5	0.0	37 (45.1)	0.096	0.243
	C4		0.204	0.635	0.7± 0.5	1.0	79 (65.3)	0.7± 0.5	1.0	58 (70.7)	0.396	0.286
Management of liver cirrhosis	D1	0.351	-.030	0.375	0.1± 0.2	0.0	7 (5.8)	0.2± 0.4	0.0	16 (19.5)	0.213	0.007*
	D2		0.312	0.214	0.5± 0.5	1.0	64 (52.9)	0.5± 0.5	0.0	39 (47.6)	0.344	0.441
	D3		0.090	0.352	0.6± 0.5	1.0	76 (62.8)	0.6± 0.5	1.0	47 (57.3)	0.397	0.839
	D4		0.200	0.291	0.7± 0.4	1.0	90 (74.4)	0.6± 0.5	1.0	47 (57.3)	0.427	0.017*
	D5		0.012	0.390	0.3± 0.5	0.0	36 (29.8)	0.2± 0.4	0.0	14 (17.3)	0.277	0.078
	D6		0.187	0.295	0.4± 0.5	0.0	50 (41.3)	0.5± 0.5	1.0	43 (52.4)	0.347	0.124
	D7		0.198	0.291	0.7± 0.5	1.0	84 (69.4)	0.5± 0.5	1.0	42 (51.2)	0.309	0.001*
	D8		0.132	0.327	0.2± 0.4	0.0	19 (15.7)	0.2± 0.4	0.0	18 (22.0)	0.249	0.359

• Note: *statistically significant at p<0.05

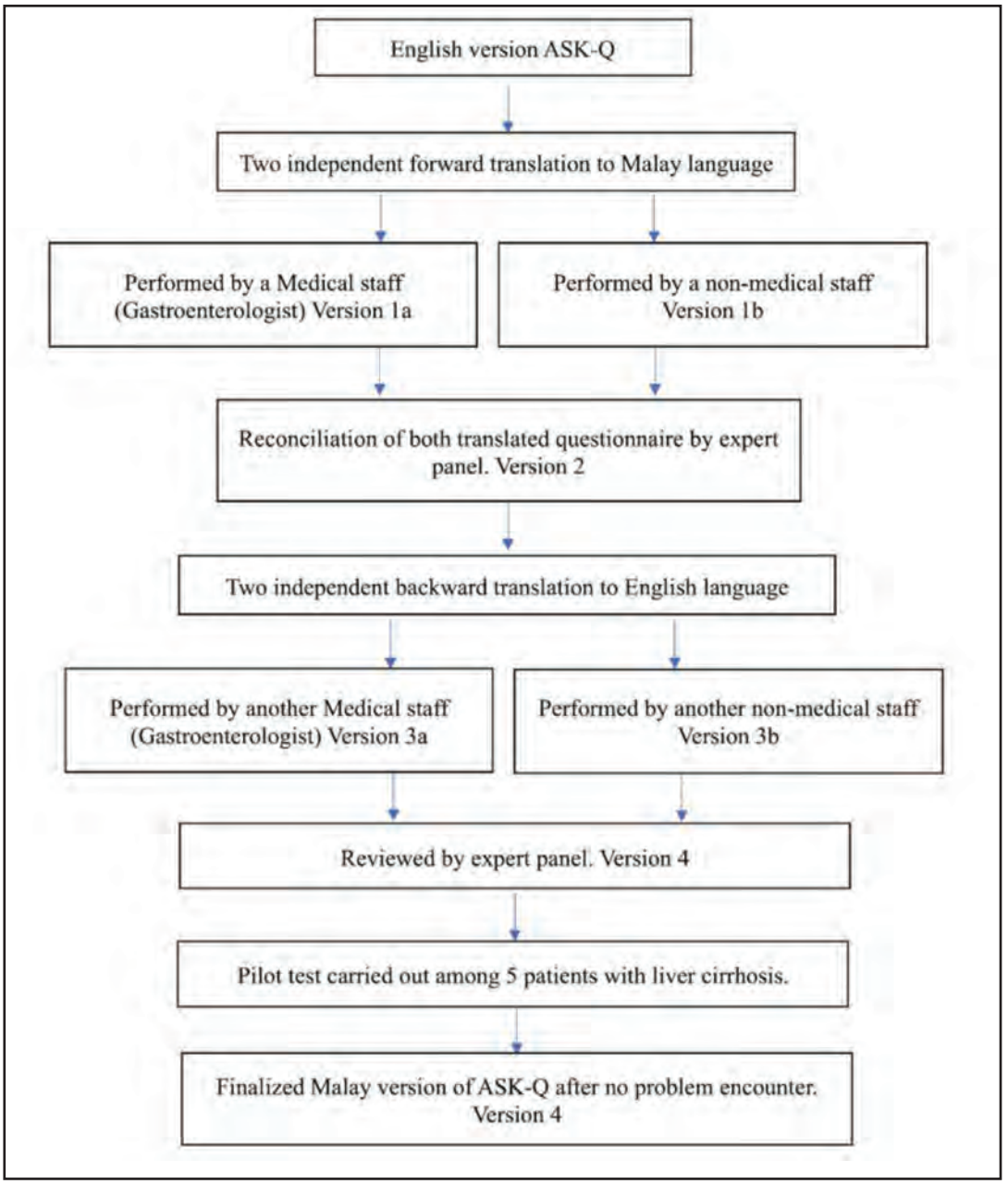

Fig. 1: Translation process of the Malay Asian cirrhosiS Knowledge Questionnaire (ASK-QM)

Patients with tertiary education had a significantly higher median score compared to those without (63.6 [45.5-77.3] vs 52.3 [36.4-63.6], p <0.05) (Table II).

Reliability

The overall Kuder Richardson was 0.761, whilst the Kuder Richardson values for each domain ranged from 0.351 to 0.585 (Table III). Seven out of 22 items had corrected item-total correlations <0.2 (Table III).

A total of 82 out of 121 patients participated at the retest (response rate=67.7%). Thirty patients (24.8%) could not be contacted and nine patients (7.5%) declined participation. Kappa values at the test-retest ranged from 0.096 to 0.632. One out of 22 items (4.5%) was in good agreement, 6 out of 22 items (27.3%) were in moderate agreement, 12 out of 22 items (54.5%) were in fair agreement and 3 out of 22 items (13.6%) were in poor agreement. Eighteen out of 22 items had Wilcoxon signed-rank test values that were statistically not significant, p>0.005 (Table III).

DISCUSSION

The ASK-QM was culturally adapted and translated from the ASK-Q using ISPOR guidelines and was found to have adequate psychometric properties.[30] ASK-QM was a moderate to good fit model.[22-25] We were unable to compare our findings to the English ASK-Q or to any other previously developed questionnaires as CFA was not performed in these studies. CFA was used over exploratory factor analysis (EFA) because EFA is used during the initial stages of questionnaire development, especially the construct of the questionnaire

remains unclear. However, CFA was performed on the ASK-QM to confirm the model's fit in the target population.[31]

The overall difficulty factor of ASK-QM was 0.5. Our findings were similar to the ASK-Q (which also scored 0.5), indicating that the questionnaire was moderately easy for a patient to answer.[32] There were 2 items in ASK-QM categorized as "too hard", while ASK-Q only reported one item as "too hard". Therefore, the ASK-QM was an adequate and well-structured questionnaire, instead of being too difficult (which may overwhelm patients) or too easy (which would deter patient knowledge acquisition).[33]

The overall total knowledge median score [IQR] of ASK-QM was 54.5 [38.6-68.2], which was slightly lower than the English ASK-Q which had a median score [IQR] of 59.1 [45.6-68.2].[17] This could be attributed to the background educational level of the patients who answered the English ASK-Q, where more 48 patients (43.6%) had tertiary education, compared to 22.3% who answered the ASK-QM.[17] Our findings were similar to studies conducted by Volk et al. with a median score of 53% and Ramachandran et al. of 56%.[6,15]

ASK-QM was able to discriminate between patients with and without tertiary education. Our findings were similar with previous studies that showed that patients with higher education levels had higher levels of self-awareness of their general health and preventive care.[34] Several studies have also reported that higher education levels were associated with a greater knowledge of liver cirrhosis.[17,35,36]

Overall, the ASK-QM had adequate internal consistency (KR=0.761).[27] All domains showed adequate internal consistency except domain D (disease management) which had a KR value of 0.351. As a comparison, domain D in the ASK-Q scored 0.528. This could be due to patients guessing their answers, hence may reduce the internal consistency value.[37] Studies have suggested removing negative point biserial or adding item numbers could markedly improve KR value.[38] However, we decided to maintain the number of items in the ASK-QM as this questionnaire should mirror the ASK-Q, so that patients could have the option of answering the questionnaire in English or Malay.[39]

Eighteen out of 22 items were not significant at test-retest in the ASK-QM, indicating adequate reliability. On the other hand, the ASK-Q showed that 15/22 items were not significant. Similarly, patients also actively looked up information after the initial administration of the ASK-Q.[17] So we selected the duration of 2 weeks so as to minimise the chances of a patient learning new things or looking up information within this 2 week period, although we cannot prevent patients from doing so.[40]

The strength of our study was that the sample size was adequate, which allowed us to assess the psychometric properties of the ASK-QM. In addition, our study sample was obtained from two large gastroenterology/ hepatology centres, and was therefore more representative of the wider Malaysian population with liver cirrhosis. The ASK-QM had a good response rate, indicating that the questionnaire was easy to administer. However, one of the limitations of this study was that we administered the ASK-QM face-to-face at baseline and via the telephone at retest and that participants could have looked up the correct answers in between the test and retest. Telecommunication using phone calls at retest was used to increase the participation rate during the retest, especially during the COVID-19 pandemic.

CONCLUSION

The ASK-QM was found to be a valid and reliable questionnaire to assess patients' knowledge of liver cirrhosis among Malay-speaking adults in this country. As mentioned before, the outcome of cirrhosis is not only dependent on the treatment administered by the clinician. Patient adherence to clinic visits, endoscopy and imaging appointments, and compliance with medication will help improve outcomes and reduce hospitalisation. It is anticipated that the ASK-QM would facilitate such adherence and improve patient compliance with therapy.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Appendix

Soal Selidik Pengetahuan Sirosis Dewasa (ASK-QM). No. Siri_____

Sila tanda pada kotak yang berkenaan:

A. Apakah yang anda faham dengan istilah “sirosis hati” (pengerasan hati)?

		Benar	Tidak Benar	Tidak Tahu
A1	Sirosis hati hanya boleh disembuh dengan ubat-ubatan.			
A2	Jangka hayat pesakit sirosis hati akan menjadi pendek setelah komplikasi berlaku.			
A3	Terdapat kerosakan kekal pada hati.			
A4	Anda tidak akan mengalami sebarang simptom jika sirosis hati masih di peringkat awal.			
A5	Sirosis hati boleh tersebar di kalangan ahli keluarga yang mempunyai kontak rapat dengan pesakit sirosis hati.			

B. Apakah sebab-sebab utama “sirosis hati”?

		Benar	Tidak Benar	Tidak Tahu
B1	Pengambilan minuman beralkohol berlebihan untuk bertahun-tahun.			
B2	Lemak berlebihan yang terkumpul dalam hati (hati berlemak).			
B3	Jangkitan virus jangka panjang seperti Hepatits B atau C			
B4	Merokok secara berlebihan untuk bertahun-tahun.			
B5	Jangkitan virus jangka pendek seperti Influenza atau Hepatitis A.			

C. Sirosis hati boleh menyebabkan komplikasi- komplikasi seperti berikut.

		Benar	Tidak Benar	Tidak Tahu
C1	Pembengkakan abdomen yang disebabkan oleh pengumpulan cecair berlebihan di abdomen (asites).			
C2	Pembengkakan saluran darah (varises) pada perut atau usus.			
C3	Keliru atau mengantuk.			
C4	Kanser hati.			

D. Bagaimanakah sirosis hati dirawat oleh doktor anda?

		Benar	Tidak Benar	Tidak Tahu
D1	Semua pesakit dengan sirosis hati perlu dirawat dengan diuretik (ubat yang meningkatkan kadar buang air kecil) untuk mencegah pengumpulan cecair.			
D2	Propranolol dipreskrib untuk mengelakkan berlakunya pendarahan daripada saluran darah yang bengkak (varises) pada esofagus (saluran makanan ke perut) atau perut.			
D3	Hanya pemindahan hati boleh merawat sirosis hati.			
D4	Endoskop bahagian atas (satu skop dimasukkan ke dalam bahagian perut) dilakukan untuk mengesan pembengkakan saluran darah (varises) pada esofagus (saluran makanan ke perut) atau perut.			
D5	Untuk pesakit dengan asites, tiada pengawalan garam diperlukan.			
D6	Hati yang sihat boleh dipindahkan daripada seseorang yang baru meninggal dunia kepada pesakit yang mempunyai sirosis hati.			
D7	Pemeriksaan ultrasound pada abdomen dilakukan untuk mengesan kanser hati.			
D8	Pemeriksaan ultrasound pada abdomen dilakukan untuk mengesan pengumpulan cecair dalam abdomen (asites).			

Complementary feeding based on local-food to improve mother ability in fulfillment nutrition stunted children

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ABSTRACT

Introduction: Mothers have the ability to provide adequate nutrition for their children. The role of providing nutrition to children aged 6-24 months who are stunted correlated to the mother's ability to provide proper nutrition. The role of mother can be carried out using the ability, confidence, and self-capacity to complete tasks, managing and providing nutrition to children aged 6-24 months who are stunted. This study aimed to analyze complementary feeding based on local food to improve the mothers' ability to fulfill their needs in stunted children.

Materials and Methods: A pre-experiment design was used to obtain data regarding 180 mothers who participated in this study. The complementary feeding based on local- food was conducted for 9 weeks, comprising 2 weeks pre-intervention, 6 weeks of intervention, and one-week post-intervention. The intervention consists of 12 sets of recipes to be made by mothers and given to their children 4 times daily over 6 weeksinstrument using Infant and Young Children Feeding Practice and Structure questionnaire. Data analysis in this study used Wilcoxon Signed Rank Test.

Results: The result of this study showed that complementary feeding based on local- food could give the impact mothers ability in food preparation and processing before complementary feeding (Z=11.644 and p-value=0.000), supplemental feeding (Z=-11.641 and p-value 0.000), and responsive feeding (Z-11.640 and p-value 0.000). The role of feeding responsiveness in accelerated growth. These results prove that self-feeding and maternal verbal responsiveness can be increased by targeting specific behaviours with appropriate behaviour change modeling and coaching practice strategies.

Conclusion: These results provide evidence that focusing on specific behaviours and implementing modification techniques such as modeling and coached practice, complementary feeding based on local food, self-feeding, and maternal verbal responsiveness can be improved.

KEYWORDS:
Complementary feeding, local food, mother ability, nutrition, stunted

INTRODUCTION

The ability of the mother to provide nourishment is intimately linked to feeding during the first two years of life. The risk of nutritional issues arises throughout this age range due to transitioning/weaning and baby feeding patterns, particularly regarding food diversity, diet quality, availability of nutrient-dense food, illness exposure, and inadequate sanitation.[1-3] In practice, mothers provide food to children based on the hunger response expressed by the child, in addition to the food menu prepared based on the wishes of the child and the use of instant complementary foods, which are considered more practical.[4–6] Responsive feeding is the ability of mothers or caregivers to actively and responsively feed children, including age-appropriate feeding methods, setting examples of healthy habits, encouraging children to eat, responding to lack of appetite, feeding in a safe environment, and using positive interaction.[7,8]

Feeding for children aged 6-24 months must be considered both in quality and quantity because during this period, children will find it difficult to switch from breastfeeding to supplementary breastfeeding or complementary foods, as well as introductions to family food for children aged over one year.[9,10] Mother's knowledge and skills are essential as a basis for fulfilling child nutrition; mothers must be able to apply parenting in terms of providing food to children (responsive feeding), which includes feeding according to the child's age, mother's sensitivity regarding the child's eating time, creating a good child's eating atmosphere and comfortable.[11,12] In the Global Strategy for Infant and Young Child Feeding, to achieve growth and development in children, mothers only give breast milk or exclusive breastfeeding until they are six months old, continue breastfeeding until they are 24 months old, and provide complementary foods for breast milk or supplemental breastfeeding. Insufficient nutritional needs are usually associated with insufficient food quantity or the presence of infection, but research shows it can occur due to various factors including parenting patterns, specifically the pattern of feeding children.[13-15]

The appropriate feeding behaviour for toddlers does not only look at the type of food provided but also includes the method, place, and time of feeding and the person who feeds it, also known as the concept of responsive feeding as

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regulated by WHO and UNICEF (2014). The practice of responsive feeding increases food acceptance and the ability to eat alone, besides that, responsive feeding includes psychosocial concepts that are good for children's mental and cognitive development.[16] Feeding practices, also known as controlling or responsive feeding practices, are actions mothers take to affect the foods their children consume. It has been demonstrated that responsive feeding techniques help kids accept new foods and develop their capacity to control how much energy they consume. To encourage healthy eating, mothers misguidedly set an example for their children by giving them energy-dense items as prizes after finishing all of their food and complimenting them. Restrictive feeding methods are linked to negative consequences, including eating meals high in energy, losing control over one's eating habits, and fussy or emotional eating.[17]

Mothers have not been trained or educated on nutrition and feeding practices but want children to have the best care and to be healthy. Mothers have expressed the need to learn strategies to encourage children to try new foods such as fruits and vegetables, manage children's food refusal, and desire to promote health. It may improve mothers' ability to practice feeding and positively impact children's nutrition. Therefore, the purpose of this study is (1) the mother's behaviours about complementary feeding before the intervention, (2) the mother's behaviours about complementary feeding after the intervention, and (3) the effectiveness impact of training on complementary feeding.

MATERIALS AND METHODS

Design and participant

This type of research is a pre-experimental design. The research design was used to analyze the effectiveness of the intervention training on complementary feeding. Research try to explain the research variable and examine the effect between variables. The impact of complementary feeding based on local-food on mother's behaviour in fulfilment nutrition stunted children. This study was conducted among mothers who have children aged 6-24 months in Public Health Centre Malang Regency, East Java, Indonesia. The population in this research are mothers who have stunted children aged 6-24 months. This study will be sampled using cluster sampling from February to June 2024. A total of 180 respondents are mothers who have stunted children ages 6-24 months participated in the study. The sampling technique in this research used randomized (cluster sampling) to recruit the participant. The sample was recruited from 6 subdistricts in rural areas with public health centers. Inclusion criteria are mothers who have stunted children aged 6- 24 months and mothers breastfeeding exclusively and registered in Integrated Health Care (in Indonesia called Posyandu). Exclusion criteria: mothers did not live at home with children and not prepare food for children.

Procedure

In conducting the research, respondents received standard care from the public health center and was given complementary feeding based on local-food intervention (used module). Complementary feeding based on local- food uses the protocols and measures outlined in the Indonesian Ministry of Health National Guidelines for Complementary Feeding. Complementary feeding based on local- should meet the following requirements: food ingredients are easy to obtain, easily processed, affordable, acceptable targets with good nutrient contentswith nutritional adequacy target and quality proteins. The program guidebook manual outlined complementary feeding based on local food activities. The complementary feeding based on local food was conducted for 9 weeks, comprising 2 weeks pre-intervention, 6 weeks of intervention, one week post-intervention, and 1 week for evaluation. Intervention consists of 12 sets of recipes to be made by mothers and given to their children 4 times daily over 6 weeks. The manual book contains WHO growth chart standard for children and recipes based on local- food as an addition to breast milk. The recipes are arramge based on selection of foodstuff, foodstuff calculation, the processing of foodstuff, how to serve food, and how to feed the children. After 8 weeks, the mothers' behaviour was observed to observe every indicator in complementary feeding.

Instrument

The main independent variable was complementary feeding based on local- food, which was assessed through a questionnaire from Infant and Young Children Feeding. Additionally, several other independent variables were under consideration, such as age, education, family type, income, and occupation. The dependent variable mother's ability to fulfill nutrition, stunted children with indicator breastfeeding, food preparation and processing, complementary feeding, and responsive feeding. Retrieval of research data used a questionnaire taken from the modification of infant and young children feeding where the instrument has been tested for validity and reliability. The validity of this research instrument obtained a value of r= 0.344, and the reliability showed that Cronbach's alpha result was 0.922 (reliable).

Data analysis

Descriptive analysis for categorical data used the frequency distribution, and for numerical data used the mean, standard deviation (SD), minimum (min) and maximum (max) value. Data were analyzed using the Kolmogorov Smirnov data normality test with p-value=0.003 so that the data was not normally distributed, and further data analysis used the Wilcoxon Signed Rank Test.

Ethical consideration

Respondents were given informed consent by signing a consent letter as a research subject for interviews and filling out questionnaire. Researchers delivered informed consent and explained the research objectives, voluntarism, and the ability to understand the information. This study received ethical approval from the Health Research Ethics Commision of the Faculty of Nursing Universitas Airlangga with protocol number 2574/KEPK/2023. Participant provided written consent for participation before data collection.

Table I:Demographic characteristic

Variable	Category	Frequency (person)	Percentage (%)
Personal factor			
Mother's age	17-25 years	51	28
	26-35 years	89	49
	35-45 years	40	22
Occupation	Housewife	155	86
	Employee	25	14
Education	Higher education	21	12
	Senior high school	84	47
	Junior high school	62	34
	Elementary school	13	7
Motivation	Strong motivation	77	43
	Low motivation	103	57
Mobility	High mobility	118	66
	Low mobility	62	34
Decision making	Good	9	5
	Enough	2	1
	Less	169	94
Knowledge	Good	99	55
	Enough	45	25
	Less	23	13
Self- esteem	High	180	100
	Low	0	0
Self- efficacy	Confidence	167	93
	Insecure	13	7

Table II:Complementary feeding on mother's behaviours in stunted children

No	Variable	Pre-couching	Post-couching	Z score	p-value
1	Food preparation and processing	35.17 ± 4.49	38.077 ± 1.23	Z= 11.644	0.000
2	Supplementary breastfeeding	63.23 ± 6.53	65.73 ± 4.10	Z= 11.641	0.000
3	Responsive feeding	44.20 ± 4.25	73.46 ± 6.27	Z=11.640	0.000

RESULTS

The study was carried out in the Malang District Health Centre with mothers under five with children aged 6-24 months experiencing stunting who participated in Integrated Health Service activities in the working area of the Malang District Health Centre, namely Tajinan Health Centre, Kepanjen Health Centre, Singosari Health Centre, Wajak Health Centre, Bululawang Health Centre in accordance with the recommendations. Five health centers were selected based on the highest number of stunting cases and randomly selected.

In the Malang Regency area, the main economic source of the community is the agribusiness sector, which includes agriculture and plantations including vegetables (tomatoes, cabbage, carrots, mustard greens, cabbage, beans, long beans, cucumbers, potatoes), rice, sugar cane, ornamental plants, wood, jabon wood, etc. In addition, Malang district is an area with livestock products, including native chicken meat and eggs, purebred chicken meat and eggs, dairy cow's milk, goat meat and milk, rabbit meat. And is an industrial area that is mostly engaged in the processing and trading of agricultural products including the refined sugar industry, the tea industry, the processed food industry (fruit chips, potato chips, and various snacks), the cutting and wood processing industry, the milk processing industry, the chicken meat processing industry.

From the Table I show that sociodemographic characteristic from personal characteristic are age, majority mothers age 25-35 years old as 49%. Mother's behaviour in fulfilling nutrition in stunting children was measured twice before and after the health coaching intervention on complementary feeding. Mentoring efforts were carried out for 2 weeks in providing nutrition to children, starting from food preparation and processing, feeding infants and children, and responsive feeding. From the results of the study, it was found that there were differences in food preparation and processing after being given a health coaching intervention with a value of Z=11,644 (p-value=0.000), supplementary breastfeeding with a value of Z-11,641 (p-value=0.000) and responsive feeding with a value of Z=11,640 (p-value=0.000)

DISCUSSION

Mother's responsive feeding behaviour in children aged 6-24 months. The working area of the Malang Regency Health Centre found that the responsive feeding behaviour of mothers in children aged 6-24 months was almost entirely well-behaved 67%, less behaved as much as 27%, and a small part well-behaved 6%. According to Notoatmodjo (2012), behaviour is a person's response or reaction to a stimulus (stimulus from outside).[18] Stimulus is a factor from outside a person (external factor), and response is a factor from within the person concerned (internal factor). Human

behaviour is included in three domains according to the purpose of education. In development, the Boom theory was modified to measure health education outcomes: Knowledge, Age, and Action.[18] According to the researcher, the responsive feeding behaviour of 20 respondents out of 30 respondents has sufficient behaviour to have positive awareness and attitude, which is obtained through eyes and ears and knowledge, possibly influenced by several factors, namely age, education, experience, and sources of information.

The mother's responsive feeding behaviour is related to education and age factors. A person's level of maturity and strength will be more mature in thinking and working, and in late adulthood, will be less sluggish in thinking because of the aging factor compared to early adulthood who are faster in thinking, receiving information, and applying information. compared to adulthood. According to researchers, the mother's responsive feeding behaviour affects a person's age and knowledge because, the older a person gets, the better the knowledge he has. This is because as a person ages, there will be physical and psychological changes. On the psychological or mental aspect, a person's mindset will become more mature and mature, so it will be easier to accept the information provided. A person's memory is also influenced by age. From the results of the study, it was found that the mother's behaviour towards responsive feeding was very influential on the growth and development of children aged 6-24 months. Less than 8 people (27%) behaved badly and 1 person (3%). Experience is an event or events that have been experienced by someone in interacting with their environment. A person's experience can be drawn from his education and work environment. Education level is one of the factors that influence or make a person's perception of ideas and technology more acceptable. According to the researcher, the mother's experience regarding responsive feeding has sufficient behaviour due to the knowledge and experience that can be taken from work directly or indirectly, on the data that has sufficient behaviour, namely not working.

Studies conducted show that there is a relationship between the mother's ability to fulfill nutrition and the growth of children aged 6-24 months.[19,20] The mother's role is very important to fulfil the nutritional needs of children, stimulating and monitoring children's growth and development. Early detection and routine growth monitoring in health care facilities is important in preventing malnutrition in children. With earlier screening in terms of measuring weight, length or height, the child's head circumference, where the risks include chronic malnutrition and stunting, it is hoped that the earlier the treatment is, the better the prognosis.[21,22] The mother's role is the main efforts to prevent and recognize stunting in toddlers. Mothers can monitor their children's growth and development by weighing them and measuring their height regularly through integrated health service activities and record medical status into health of mother and child book.

Nutritional disorders in infants and children are generally caused by poor quality and poor food feeding patterns. The mother's ability to provide food results in nutritional disorders experienced by the child which results in impaired child growth, which is caused by not being given breast milk, giving supplementary feeding too early and generally not containing enough macro and micro nutrients.[23,24] Apart from that, looking at the pattern of caring for children's food by mothers, there are still many mothers who provide prelacteal food or provide complementary feeding too early, and the quantity and quality of the nutrients provided is inadequate.[25]

The cause of growth disorders in children include incorrect and inappropriate provision of supplementary feeding as well as not meeting nutritional requirements both in terms of quantity and type in children aged 6-24 months, where this age period is a critical growth period so it needs to receive more special attention is needed. Research shows that maternal factors greatly influence nutritional status, and children born to mothers with higher education have better nutritional status than children born to mothers with low education. In addition, there are intergenerational consequences of early marriage on the welfare of children because they were born in an unsettled family's economic condition, thus affecting the development and health of children. After all, mothers are not able to meet their nutritional needs properly. The type of work and socioeconomic status, especially those who work in the agricultural sector, and also live in rural areas have a higher risk than urban residents.

Maternal autonomy in decision-making where is a factor related to maternal empowerment, especially about child health. A mother's ability to make decisions becomes a strength in maintaining health and providing household needs so that the nutritional needs of families, especially children, can be met properly. Mother's knowledge can be a barrier. In addition, related to the mother's motivational barriers, sometimes mothers feel tired, bored, feel unsure of being able to carry out their duties and roles in fulfilling nutrition for children who experience stunting. In practice, mothers provide food to children based on the hunger response expressed by the child; besides that, the food menu is prepared based on the wishes of the child, and the use of instant complementary foods are considered more practical.

The intervention of providing complementary feeding based on local food is carried out by utilizing existing local food ingredients with the use of resources owned by the family in using empty land at home as a yard. In the public health center of Wagir in Malang Regency, East Jawa, Indonesia is mostly an agricultural area such as cattle, poultry and fisheries. So it is hoped that resource utilization can be utilized optimally. Based on the research results, it show that complementary feeding based on local food can influence the mother's ability to optimally feed babies and children with indicators of food preparation and processing, feeding babies and children, responsive feeding.

This is in accordance with the recommendations for Infant Young Child Feeding (IYCF) and guidelines for feeding infants and children by the Ministry of Health (2018) where the principles of feeding infants and children include being timely, adequate, safe, and given in the correct way. Timeliness in terms of IYCF is that supplementary feeding is

given when the need for breast milk can no longer meet the baby's nutritional needs, where at the age of 6 months the child can start to be introduced to supplementary feeding. Adequate in terms of IYCF is that supplementary feeding is able to meet sufficient energy, protein and micronutrients to achieve child growth and development by considering age, quantity, frequency, consistency/texture and food variety. safe in terms of IYCF where supplementary feeding is prepared and stored in a hygienic manner, given by hand and using clean equipment. given in the correct way, in this case responsive feeding, where supplementary feeding is given on a scheduled basis, with a supportive environment and proper feeding procedures.

Infant and young children aged 6-24 months need proper food intake to achieve optimal growth and development, especially in the first 1000 days of life. Unmet nutritional needs result in babies and babies experiencing malnutrition, poor nutrition, stunting, wasting, suboptimal brain intelligence, decreased immune system and problems with stunted growth and development, even death. In babies aged 0-6 months, nutritional needs are met through exclusive breastfeeding. The content of carbohydrates, protein, fat, vitamins, minerals, cholesterol, vitamin D and fluorine contained in breast milk means that babies aged 0-6 months get a balanced nutritional intake. Entering the age of 6 months, babies already receive complementary foods to fulfill their nutritional intake. Digestion is starting to be ready to consume complementary foods for breast milk or supplementary feeding, so children can start to be given complementary foods such as biscuits or milk.[19,20,26]

Once the baby is more than 6 months old, the need for food intake is not only sufficient through breast milk. Complementary foods for breast milk need to be given to babies gradually depending on the type, quantity and texture according to the baby's age, meanwhile giving breast milk to children does not need to be stopped until the child is 2 years old. Supplementary feeding can be given to children according to the child's age, where at the age of 6-9 months the child can be given food with a soft or mashed texture, at the age of 9-12 months he can be given food with a soft texture such as strained porridge or steamed rice, and at the age of 12-24 months can be given food with a solid texture, where previously you can start with coarsely chopped food and gradually adjust it to the child's abilities until the food menu can be adjusted to the family menu.[23,24,27]

When introducing breastfeeding to children, it is recommended that in the first 2 weeks at most, porridge and single fruit be introduced with a food frequency of 1-2 times a day. This introductory period is used to introduce various sources of carbohydrates, vegetables and fruit. In the following week, children should be introduced to protein, both animal and vegetable protein and additional sources of fat in the form of fine/strained porridge which is given along with carbohydrates and vegetables with a food frequency of 2-3 times a day and they should be introduced to snacks. This principle of food variation is the basis for compiling a daily menu so that children's macro and micronutrient needs can still be met. Meanwhile, the parenting pattern in providing food in this case is responsive feeding. Responsive feeding when feeding, respond to the child with a smile, maintaining eye contact, encouraging positive words, and giving the child soft food that can be held to stimulate active self-eating (finger snacks).

CONCLUSIONS

The result of this study showed that the impact of food preparation and processing before complementary feeding based on local-food, complementary feeding, and maternal responsiveness.The role of feeding responsiveness in accelerated growth. These results provide evidence that self-feeding and maternal verbal responsiveness, can be increased by targeting specific behaviours with appropriate behaviour change strategies of modeling and coached practice. Therefore, the source of food for complementary feeding must be accessible to all communities.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Integrating CCL2 and TNF-α into the Framingham Risk Score for cardiovascular risk prediction: a cross-sectional study in a Malaysian cohort

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are the leading cause of death worldwide, significantly contributing to increased healthcare costs and deteriorated health. In Malaysia, CVDs account for 20.79% of deaths in government hospitals. Key risk factors include high blood sugar levels, elevated blood pressure, and increased cholesterol levels. Atherosclerosis frequently serves as the underlying condition for coronary heart disease (CHD), with CCL2 and TNF-α playing a crucial role in recruiting immune cells to inflammation sites. Early diagnosis of CVDs risk is important for preventing severe complications. This cross-sectional study aims to investigate the relationship between biomarker CCL2 and TNF-α expression levels and Framingham Risk Score (FRS) categories in a Malaysian cohort.

Materials and Methods: A total of 333 patients from the Family Medicine Specialist Clinic at Hospital Sultan Abdul Aziz Shah were recruited between March 2022 and February 2023. Blood samples were taken after a 12-hour fasting period, and levels of fasting blood sugar (FBS), triglycerides (TG), total cholesterol (TC), HDL cholesterol, and LDL cholesterol were measured. 150 plasma samples were randomly selected for cytokine analysis of CCL2 and TNF-α using the Human Magnetic Luminex Assay. Patients' cardiovascular risk was assessed using the FRS calculator. The Kruskal-Wallis test was used to analyze the relationship between cytokine levels and FRS categories, followed by a post hoc test with Bonferroni correction. A logistic regression model was implemented to assess the independent effects of these variables.

Results: The results demonstrated a significant association between the level of chemokines CCL2 and pro-inflammatory TNF-α, and FRS categories (low-risk, moderate-risk, and high-risk). CCL2 levels were notably higher in the high-risk group, as were TNF-α levels, with both biomarkers showing increasing trends with higher risk categories, (p<0.001, effect size=0.32) and (p<0.001, effect size-0.29), respectively. Multiple logistic regression analysis showed that dyslipidaemia, FBS, and TNF-α remained significant after adjusting for other variables. Specifically, dyslipidaemia had lower odds of being in the high-risk group (AOR: 0.04), while FBS (AOR: 3.19) and TNF-α (AOR: 1.18).

Conclusion: This study highlights the potential of CCL2 and TNF-α as biomarkers for CVDs risk assessment. Integrating these biomarkers into CVDs risk prediction models may enhance the precision of identifying individuals at elevated risk. However, the study's cross-sectional design and small sample size for cytokine analysis constrain the findings. Future research should explore the long-term predictive value of these cytokines in larger, longitudinal cohorts and explore more advanced techniques for improving CHD risk prediction models.

KEYWORDS:
Cardiovascular diseases, atherosclerosis, Framingham Risk Score, CCL2, TNF-α

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and have contributed significantly to increasing healthcare costs and deteriorated health. In Malaysia, CVDs are the number one factor of mortality contributing to 20.79% among the top ten causes of death in government hospitals, according to Malaysian Health Facts 2023.[1] Significant risk factors associated with CVDs include high blood sugar levels, elevated blood pressure, and increased cholesterol levels.[2] These factors are known to drastically increase the risk of developing CVDs, such as heart disease and stroke.

Atherosclerosis frequently serves as the underlying condition for coronary heart disease (CHD). CCL2 plays an important role in migrating various immune cells, such as monocytes, macrophages, and T lymphocytes to the inflammation site.[3] The association between CCL2 and atherosclerosis has been studied since 1991 until the present when researchers found out that CCL2 expression was relatively higher in atherosclerotic vessels than in normal vessels.[4] An increased expression of CCL2 has been strongly associated with macrophage infiltration across multiple layers of the arterial

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wall and subendothelial space, which causes the accumulation of the immune cells at the inflammatory site. Additionally, highly expressed CCL2 correlates with inflammatory processes in atherosclerotic lesions such as lipid deposition and fibrosis, contributing to the advanced stage of atherosclerosis.[5]

The interaction between CCL2 and its receptor CCR2 plays a critical role in monocyte recruitment, leading to their transformation into foam cells and the formation of fatty streaks in the arterial wall.[6,7] Macrophages activation triggers the release of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), promoting endothelial dysfunction, oxidized LDL accumulation, and atherosclerotic plaque rupture, leading to thrombosis and acute cardiovascular events.[8-10] By measuring TNF-α levels, we can determine the inflammatory dysregulation that contributes to arterial damage and cardiovascular events.

An early diagnosis of CVDs risk may help patients prevent severe complications and provide a personalized treatment. In Malaysia, the application of the FRS scoring system in the CVDs prediction model has been calibrated and validated for the Asian population by Chia et al.[11] However, its predictive accuracy has certain drawbacks, as it underrepresents younger individuals and excludes key factors like family history and diabetes.[12-16] This limitation underscores the need to incorporate additional biomarkers into the FRS prediction model. Therefore, this study aims to investigate the relationship between the expression level of cytokines TNF-α and CCL2, and the classification within the FRS groups in predicting cardiovascular disease risk in 10 years.

MATERIALS AND METHODS

A total of 352 patients attending the Family Medicine Specialist Clinic (FMSC) at Hospital Sultan Abdul Aziz Shah (HSAAS) located in Selangor were recruited in this study from March 2022 to February 2023. However, only 333 patients fulfilled the inclusion and exclusion criteria. Those with a diagnosis of any heart disease like having a New York Heart Association (NYHA) classification, incomplete clinical data in body mass index (BMI), and insufficient samples noticed during laboratory procedures were omitted from the study. Approval from the Institutional Ethics Board was secured from the Ethical Committee for Research Involving Human Subjects (JKEUPM-2021-700) before the start of the study. All eligible patients who participated in the study obtained their verbal and written consent.

Patients with ages ranging from 30 to 75 were recruited. The recruitment process was done by a convenient sampling method, during the early stage, where the researcher screened patients' medical histories to ensure they met the eligibility criteria. This study's inclusion criteria include adult patients 30 to 75 years old, without any cardiovascular events such as coronary heart disease or stroke. Patients with the following criteria were excluded: pregnant women, patients with a history of ischaemic heart disease and stroke, or the presence of conditions including active cancer, liver disorders, active autoimmune disease, and active thyroid. The patient's clinical data including sociodemographic data such as age, gender, race, education level, and marital status, and clinical information such as presence of chronic diseases, smoking status, the use of anti-hypertensive and lipid-lowering agents, based on their first medical entry were retrieved from patient's medical record. The patient's physical examination including systolic blood pressure (SBP) was also recorded. Due to budget limitations, 150 patients were randomly selected using a random number generator from the list of patients who met the inclusion criteria for each category. To ensure the sample represents the overall population, a randomization process was implemented to select 50 participants from each FRS category: low-risk (n=50), moderate-risk (n=50), and high-risk (n=50). This process involved using An a priori power analysis performed using g*power 3.1.9.7[17] to justify the sample size. Using a medium effect size (r=0.0588), power of 80%, and p of 0.05, g*power indicated that at least 50 participants were required.

A total of 10 mL venous samples were collected from the patients after a 12-hour fasting period. The collected blood was subjected to fasting blood sugar (FBS), level of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured. The remaining plasma was stored at -80°C for further plasma biomarker analysis. The study parameters such as gender, age, TC, HDL cholesterol level, SBP, smoking, and diabetes status were used to assess the patients' Framingham general CVDs risk score using the FRS calculator.[10] Their remaining collected blood samples were frozen at -80C for plasma biomarkers concentration measurement of CCL2 and TNF-α cytokines using Human Magnetic Luminex Assay (R&D Systems, Minneapolis, USA). The frozen plasma samples were thawed and diluted before being incubated with fluorescently labeled beads conjugated to specific antibodies for CCL2 and TNF-α. Following incubation, the beads were washed to remove unbound proteins and then incubated with a biotinylated detection antibody cocktail. After another washing step, streptavidin-phycoerythrin was added to bind the biotinylated antibodies, providing a fluorescent signal proportional to the amount of cytokine bound. The beads were then analyzed using the Luminex assay.

All statistical analyses were performed using IBM SPSS Statistics, version 29.0 (SPSS, Chicago, IL). Data are expressed as mean ± standard deviation or median (IQR) for skewed numerical data distribution. Kruskal Wallis test was performed to evaluate the relationship between cytokine level and FRS categories. Two-tailed $p<0.05$ was considered a significant difference. To evaluate the relationship between cytokine levels and FRS categories, the Kruskal-Wallis test, a non-parametric statistical method was used. This test is appropriate for comparing medians across three or more independent groups when the data do not meet the assumptions of normality. If a significant difference was observed (two-tailed $p<0.05$), it indicated that at least one group differed in cytokine levels. Further pairwise comparisons were conducted using a post hoc test with Bonferroni correction to identify specific group differences while controlling for multiple testing. Additionally, the potential confounders such as medications and comorbidities were addressed by modifying these variables in this study.

Multinomial logistic regression analysis was applied to measure parameters that were not included in FRS. In the first stage, univariate logistic regression was used to screen the potential confounders associated with FRS categories, identifying variables with a significance level of p<0.250 for inclusion in the multivariate analysis. These selected cofounders were then included in the multivariate logistic regression model to assess their independent associations with FRS categories. The results were reported as adjusted odds ratios (AOR) with corresponding 95% confidence intervals (CI) and p-values to assess the influence of each confounding factor on FRS categories.

RESULTS

From a total of 352 patients, 333 eligible patients, aged 30 to 75 years, who had no cardiovascular events and documented blood pressure, along with TC, HDL-C levels, smoking status, and presence or absence of diabetes mellitus (DM), were included. Table I shows the clinical characteristics of the total 333 patients with a median age of 55 years old, with gender distribution predominantly female (61.6%) and followed by male (38.4%). The study population is mainly represented by Malay (88%), with a smaller portion of Chinese (6.3%) and Indian (5.7%) ethnicities. Among all subjects, the prevalence of basal diseases shows a high rate of dyslipidaemia (76.6%), followed by hypertension (48.6%) and diabetes (31.8%). The FRS score analysis (Table I) showed that the population was almost equally divided into three risk categories: low-risk (37.8%), moderate-risk (26.7%), and high-risk (35.4%).

Based on the clinical characteristics of patients Table II, the average age increases with risk level, from a median of 46.50 years in the low-risk group to 62 years in the high-risk group. Similarly, the same pattern is observed in gender whereas the proportion of males increased across FRS groups, from 28% in the low-risk group to 52% in the high-risk group. In contrast, smoking prevalence is low overall, with 2% smokers in the low-risk group, and 8% in both moderate-risk and high-risk groups. Hypertension and dyslipidaemia prevalence shows an increasing trend with risk level, from 32% and 56% respectively in the low-risk group to 60% and 90% in the high-risk group. Conversely, DM is more prominent in the high-risk group (90%) compared to the low-risk and moderate-risk groups. TC levels are highest in the moderate-risk with a median of 5.66 mmol/L and lowest in the high-risk group at 4.73 mmol/L. HDL-C levels decreased with risk, from 1.32 mmol/L in the low-risk group to 1.20 mmol/L in the high-risk group but reported the highest median in the moderate-risk group (1.40 mmol/L).

To assess the relationship between FRS categories and levels of the cytokines CCL2 and TNF-α, we performed the Kruskal Wallis test. Figure 1(a) and Figure 1(b) demonstrate statistically significant differences in CCL2 and TNF-α levels, respectively, across low-risk, moderate-risk, and high-risk groups. For CCL2 (Figure 1(a)), the Kruskal-Wallis test indicates a significant difference among groups (p<0.05). Post hoc comparisons using Dunn's test show that CCL2 levels in the high-risk group are significantly higher than those in the low-risk group (p<0.001, effect size=0.32) and the moderate-risk group (p<0.050, effect size=0.15).

Similarly, for TNF-α (Figure 1(b)), the Kruskal-Wallis test confirms significant differences among the risk groups (p=0.001). Dunn's test reveals that TNF-α levels in the high-risk group are significantly higher than those in the low-risk group (p<0.001, effect size=0.46) and the moderate-risk group (p<0.05, effect size=0.29). However, the moderate-risk and low-risk groups also differ significantly (p<0.05) after applying Bonferroni correction.

To identify and quantify the association between potential confounding factors such as age, gender, comorbidities, and cardiovascular risk categories as determined by the FRS, we performed a multinomial logistic regression model. Initially, we screened the variable through univariate analysis with those showing a p-value <0.25 considered for inclusion in the multivariable analysis. While detailed data are not presented in a table, the key findings from the univariate logistic regression analysis are summarized below.

From nine potential cofounders that were screened from the univariate analysis: BMI, ethnicity, dyslipidaemia, heart rate, FBS, TG, LDL, CCL2, and TNF-α, six variables were found to be significant with a threshold of p<0.25. Dyslipidaemia and TNF-α are strongly associated with FRS groups, differentiating high-risk and low-risk groups. Both dyslipidaemia (COR: 0.14, 95% CI: 0.05–0.42, p<0.001), and TNF-α (COR: 1.24, 95% CI: 1.11–1.38, p<0.001) were more likely being in high-risk group. Similarly, FBS (COR: 3.43, 95% CI: 2.07–5.67, p<0.001), CCL2 (COR = 1.01, 95% CI: 1.001–1.10, p=0.004), TG showed a moderate association with odd ratio (COR: 1.90, 95% CI: 1.03–3.51, p=0.039), and LDL had less odd of being in high-risk group (COR: 0.59, 95% CI: 0.39–0.89, p=0.011) compared in moderate-risk group. However, BMI, ethnicity, and HR were not significant (p>0.25) and thus eliminated from further multivariate analysis.

Further analysis using multiple logistic regression analysis is summarised in Table III, dyslipidaemia, FBS, and TNF-α remained significant after adjusting for other variables. Specifically, dyslipidaemia has lower odds of being in high-risk groups, (AOR: 0.04, 95% CI: 0.01–0.28, p<0.001). Conversely, FBS (AOR: 3.19, 95% CI: 1.80–5.63, p<0.001), and TNF-α both had higher odds of being in the high-risk group (AOR: 1.18, 95% CI: 1.03–1.35, p=0.017). Other variables, such as TG, LDL, and CCL2, did not show significant associations after adjustment, indicating that their effects may be influenced by confounding factors.

DISCUSSION

This study demonstrated a significant association between higher FRS categories and elevated levels of chemokines CCL2 and pro-inflammatory cytokines TNF-α. These associations were observed in the study population presented in Table II, which highlighted the risk factors of CVDs such as age, gender distribution, smoking status, DM, hypertension, dyslipidaemia, and blood profile; TG, FBS, and HDL, in the subset of 150 participants. In this study, males at the median age of 55 years old are more susceptible to developing CHD compared to females. The findings are aligned with the previous studies in assessing gender differences in

Table I: Demographic description of the study population, N = 333

Demographic	n (%)
Age (year)	55.00 (44.00-63.00)[a]
Gender	
Male	128 (38.4)
Female	205 (61.6)
Ethnicity	
Malay	293 (88.0)
Chinese	21 (6.3)
India	19 (5.7)
Smoking	21 (6.3)
Medical illness	
Diabetes	106 (31.8)
FBS (mmol/L)	5.40 (4.95-6.50)a
Hypertension	162 (48.6)
SBP (mmHg)	134.67 ± 16.11e
Dyslipidaemia	255 (76.6)
Total cholesterol (mmol/L)	5.33 (4.52-6.10)a
High-density lipoprotein (mmol/L)	1.37 (1.17-1.60)a
FRS	
Low	126 (37.8)
Moderate	89 (26.7)
High	118 (35.4)

[a]: median (IQR: 75-25). [e]: mean ± SD.
FRS: Framingham Risk Score
FBS: Fasting Blood Sugar
SBP: Systolic Blood Pressure

Table II: Patients' clinical characteristics according to FRS categories, N= 150

Demographic	Low (%) (n=50)	Moderate (%) (n=50)	High (%) (n=50)
Age (year)	46.50(40.25-54.25)[a]	59.0(50.75-64.0)[a]	62.0(54.0-67.0)[a]
Gender			
Male	14(28)	21(42)	26(52)
Female	36(72)	29(58)	24(48)
Ethnicity			
Malay	42(84)	42(86)	42(88)
Chinese	4(8)	5(10)	2(4)
India	4(8)	2(4)	4(8)
Smoking	1(2)	4(8)	4(8)
Medical illness			
Diabetes	0	0	45(90)
FBS (mmol/L)	5.00 (4.71-5.38)[a]	5.27(4.81-5.84)[a]	7.20(5.98-8.78)[a]
Hypertension	16(32)	26(52)	30(60)
SBP (mmHg)	125.68 ± 13.88[e]	141.14 ± 17.55[e]	137.34 ± 13.19[e]
Dyslipidaemia	28(56)	38(76)	45(90)
TC (mmol/L)	5.38(4.98-6.17)[a]	5.66(4.95-6.62)[a]	4.73(3.75-5.85)[a]
HDL-C (mmol/L)	1.32(1.13-1.61)[a]	1.40(1.20-1.60)[a]	1.20(1.07-1.50)[a]

[a]: median (IQR: 75-25). [e]: mean ± SD
FRS: Framingham Risk Score
FBS: Fasting Blood Sugar
SBP: Systolic Blood Pressure
TC: Total Cholesterol
HDL-C: High-Density Lipoprotein

determining CVDs risk. A study revealed that the incidence of low, moderate, and high-risk CVDs among men is significantly higher than among women ($p<0.05$).[18] Several factors could contribute to the pathogenesis of atherosclerosis such as age, lifestyle, physical activities, and hormones. Males generally have a higher level of testosterone which may contribute to an increasing lipid profile and could increase the likelihood of developing CHD.[19] Additionally, the high-risk group had significantly higher age, SBP, and FBS concentrations compared to those in low-risk and moderate-risk groups. Another study has reported a similar pattern where patients with high SBP and FBS are more likely to be classified in the moderate-risk and high-risk groups of cardiovascular disease.[16]

The prevalence of hypertension and dyslipidaemia increases with higher FRS categories, with nearly 60% of high-risk individuals having hypertension and 90% with dyslipidaemia. These results reflect a common cardiovascular risk profile observed in Asian populations where factors like

Table III: Association between potential confounders on FRS using multivariate logistic regression, N=150

Potential Confounders	Moderate vs. Low		High vs. Low	
	AOR (95% CI)	p-value	AOR (95% CI)	p-value
Dyslipidaemia	0.40(0.16-1.01)	0.054*	0.04(0.01-0.28)	0.001*
FBS	1.18(0.71-1.94)	0.529	3.19(1.80-5.63)	<0.001*
TG	1.04(0.54-2.03)	0.898	1.32(0.63-2.75)	0.458
LDL	1.33(0.85-2.06)	0.210	0.61(0.35-1.08)	0.089
CCL2	1.00(0.99-1.01)	0.325	1.00(0.99-1.02)	0.277
TNF-α	1.12(1.00-1.12)	0.047	1.18(1.03-1.35)	0.017*

*: Significant. AOR: Adjusted odds ratio. vs.:Versus

Table IV: Summary of studies related to TNF-α and CCL2 expression in atherosclerosis

TNF-α			
Atherosclerotic progression	**Study Population**	**Findings**	**References**
Early-stage atherosclerosis	apoE-/-/LDL receptor-/- mice	Expression of medial TNF-α and its receptor happens before the atherosclerotic lesions	[26]
Endothelial activation	Human umbilical vein endothelial cells (HUVECs)	TNF-α enhances the movement of LDL across endothelial cells via NF-κB and PPAR-γ activation	[27]
Monocyte recruitment	CHD patients	Overexpression of TNF-α activates the monocyte recruitment forming cholesteryl ester-laden cells	[28]
Plaque destabilization	Patient with symptomatic and asymptomatic carotid stenosis	TNF-α mediates the activation of TREM-1 in VSMCs isolated from symptomatic plaque	[29]
CCL2			
Atherosclerotic progression	**Study Population**	**Findings**	**References**
Early-stage atherosclerosis	CAD patients	CCL2 inhibited the internalization of HDL phospholipids and proteins	[30]
Endothelial activation	Cell culture	CCL2 influences the effects of miR-495 on the proliferation and apoptosis of HUVECs	[31]
Monocyte recruitment	Mice mode	The highest levels of CCL2 are found in neutrophils and circulating monocytes	[32]
Plaque destabilization	Cell culture	Smooth muscle cells (SMCs) secrete CCL2 in the human atherosclerotic plaque and murine SMC line when subjected to inflammatory cytokine in vitro.	[33]

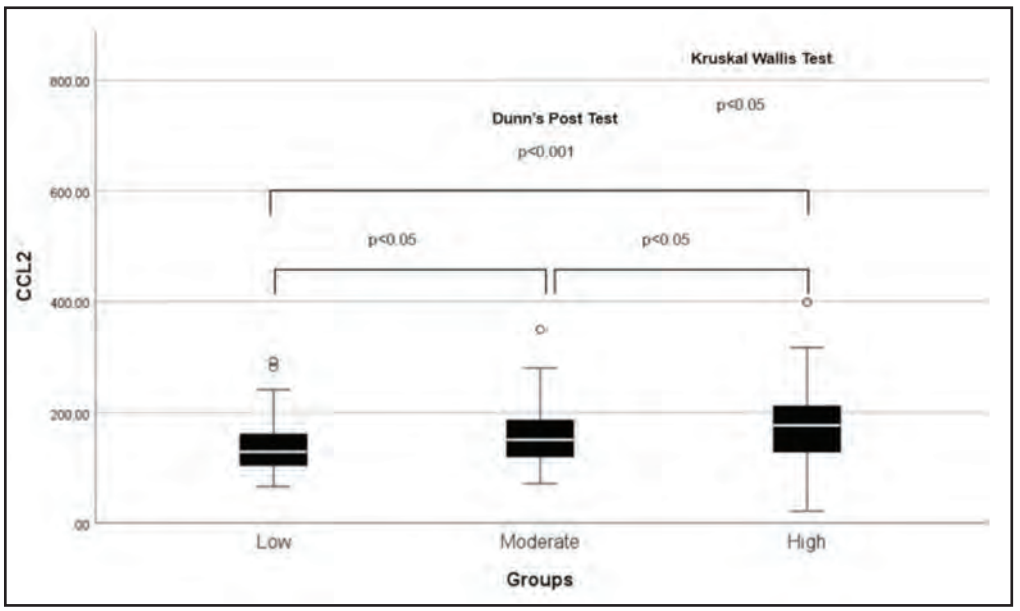

Fig. 1a: Distribution of CCL2 across FRS groups. Higher CCL2 levels in the high-risk group suggest a link to increased cardiovascular risk. Significant differences were found between low-risk vs. high-risk, and moderate-risk vs. high-risk

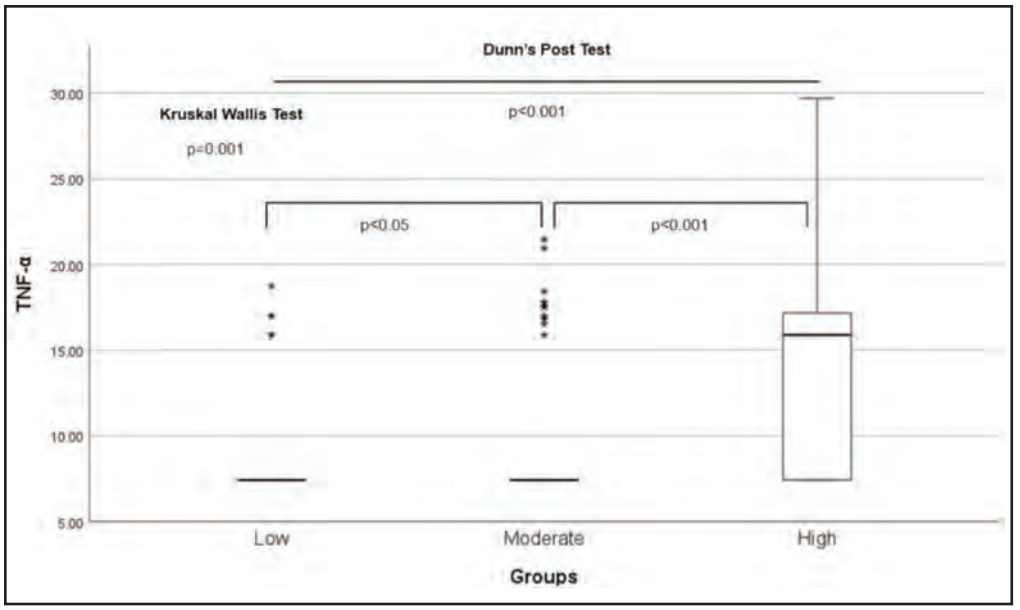

Fig. 1b: Distribution of TNF-α across FRS groups. Elevated TNF-α in a high FRS group may indicate increased inflammation with higher risk. Significant differences were observed between the high-risk and both low-risk and moderate-risk groups

genetics and individual lifestyles significantly influence cardiovascular risk.[20] Hypertension is known to contribute significantly to cardiovascular risk by promoting arterial damage and atherosclerosis. The arterial injury and plaque buildup will trigger the release of chemokines and pro-inflammatory cytokines will work together to regulate the inflammatory responses within the arterial wall.[21,6] The atherosclerotic plaque will secrete more inflammatory cytokines such as TNF-α, interleukin-1, interleukin-6, and interferon-gamma, as well as macrophages at the site of endothelial cells.[22]

As the inflammatory process progresses, CCL2 and TNF-α contribute significantly to the recruitment of immune cells to the site of plaque formation. In our study, we observed an increase in CCL2 and TNF-α levels with higher FRS categories; low-risk, moderate-risk, high-risk. However, TNF-α concentration increased relatively lower than the expression level of CCL2. This is consistent with the general understanding that both cytokines play a part in the inflammatory process, CCL2 tends to have a more prominent role in monocyte recruitment and plaque progression. In contrast, TNF-α contributes more to the inflammatory cascade amplification. The result is aligned with a previous study that showed that TNF-α plays a critical role in initiating and amplifying inflammatory responses by inducing multiple cytokines and chemokines (CCL2, CCL5, ICAM-1, VCAM-1, and IL-6).[23]

Conversely, an increased level of CCL2 will facilitate the process of oxidized LDL ingestion by macrophages to form foam cells.[22] CCL2 promotes the monocytes recruitment to the endothelial layer, where they infiltrate and differentiate into macrophages.[24] Georgakis et al. have researched human atherosclerotic plaque exploring the role of inflammatory markers including CCL2 in plaque vulnerability and progression. They found that CCL2 levels correlate with the marker of plaque instability, for example, pro-inflammatory characteristics and matrix turnover which lead to increased cardiovascular events.[25] Another study has reported a similar pattern in CCL2 expression level, where the concentration of CCL2 (>9 fold) is significantly apparent in all artery layers, particularly in adventitial tissue. The results contrast to only 26% in normal arteries and localized to smooth muscle cells.[23]

The significant associations were observed in our Kruskal-Wallis and post hoc Dunn's tests for CCL2 and TNF-α play an important role in inflammation in cardiovascular risk stratification. Increased CCL2 and TNF-α levels in high-risk categories align with other studies that highlight these markers as predictors of adverse cardiovascular events. Given their role in immune cell recruitment and inflammation, both markers offer insight into how immune activation inflammation underpins cardiovascular risk. Table IV summarises studies supporting the role of CCL2 and TNF-α mediating the inflammatory processes involved in atherosclerosis progression at various stages.[26-33]

This study also highlighted the significance of various confounders in predicting CVDs risk as assessed by the FRS. Specifically, TNF-α showed a significant odd ratio of being in high-risk groups even after adjusting for other variables, this predictor may enhance CVDs risk assessment using FRS. Our findings aligned with a previous study conducted by Yuan et al[34], demonstrating that increased TNF levels are associated with a higher risk of common CVDs, with genetically predicted TNF levels showing a positive association with CAD. While FRS provides a well-established framework for predicting CVDs risk based on parameters; age, gender, TC level, HDL, SBP, DM status, smoking, and hypertension medication. This assessment underestimates other cofounders like biomarkers, dyslipidaemia status, TG, HDL, and FBS levels which may lead to inaccurate risk assessment affecting

a patient's CVDs risk profile.[35] A similar case was reported by Qiu et al.,[36] where FRS underestimated CHD events by 22% for the total population, while overestimated for males by 152%.

The current study provides a predictive model to analyze the relationship between inflammatory biomarkers, CCL2 and TNF-α, and cardiovascular risk as stratified by the FRS. Increased levels of CCL2 have been linked to increased plaque vulnerability, while TNF-α contributes to endothelial dysfunction and the amplification of the inflammatory response, both of which are crucial in the atherosclerosis progression in all stages. Therefore, incorporating these biomarkers into risk prediction models FRS could provide a stronger and more accurate result, especially for low-risk and moderate-risk groups. To implement this predictive model into clinical practice, further studies should be conducted to validate the biomarker across diverse populations and evaluate its reliability in different clinical settings.

The strength of the current study is the comprehensive assessment of cytokine levels across a well-characterized cohort with varying cardiovascular risk profiles. The demographic and clinical data provided in Table I and Table II add depth to the analysis performed. However, several limitations of our study should be considered. Firstly, the study was conducted in a cross-sectional design, and we did not follow up with the patients over time. Secondly, the relatively small sample size of 150 for cytokine measurement may reduce the accuracy of our findings. A larger sample size would be needed to increase the sensitivity towards the association within the FRS groups. Thirdly, the study was done within a single centre, the subjects were predominantly Malay population (88%), which does not fully represent the general population. Lastly, potential confounding factors, such as underlying comorbidities and medication use, were not fully controlled, which could influence cytokine levels. Future studies should extend to longitudinal studies to establish the predictive value of CCL2 and TNF-α levels over time and may consider advanced imaging techniques and genetic implications to improve the prediction of CHD risk.

CONCLUSION

This study highlights the potential of CCL2 and TNF-α as biomarkers for CVDs risk assessment. Integrating these biomarkers into CVDs risk prediction models may enhance the precision of identifying individuals at elevated risk, hence supporting clinical intervention and personalized care management. However, the study's cross-sectional design and small sample size for cytokine analysis constrain the findings. Future research should explore the long-term predictive value of these cytokines in larger, longitudinal cohorts and explore more advanced techniques for improving CHD risk prediction models.

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A 15-year experience with keratoplasty in the management of paediatric corneal diseases: indications and clinical outcomes in Malaysia

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ABSTRACT

Introduction: Corneal blindness is a leading yet preventable cause of childhood blindness worldwide. Despite the need for corneal transplantation in paediatric cases, comprehensive data on its aetiology, clinical outcomes, and graft survival in Malaysia remain scarce. This study reviews the indications and outcomes of paediatric keratoplasty at Hospital Kuala Lumpur over the past 15 years.

Materials and Methods: We conducted a retrospective evaluation of paediatric patients (less than 12-years-old) who underwent keratoplasty in Hospital Kuala Lumpur, from January 2008 to December 2022. We analysed demographic data, preoperative diagnoses, types of keratoplasty performed, and the 1-year graft survival rate.

Results: 100 eyes from 95 patients were included in the study, with a mean age of 4.39 ±3.32 years. The indications for keratoplasty included limbal dermoid (45%), anterior segment dysgenesis/Peter's anomaly (22%), infective keratitis (14%), congenital glaucoma (4%), and other pathologies (15%). 31/100 (31%) had corneal perforation. Of the patients, 56% underwent lamellar keratoplasty (LK), while 44% underwent penetrating keratoplasty (PK). Complications included wound dehiscence (4%) and graft melting (3%). 77% completed 1-year follow-up, and the overall 1-year graft survival rate was 54.5%. Limbal dermoid showed a better graft survival rate (72.2%) compared to other pathologies (39%), with a p-value of 0.004. LK has a higher 1-year graft survival rate of 66% compared to PK (36.7%) with a p-value of 0.003. Among the cases of perforated corneas, an overall 1-year graft survival rate of 25.8% (8/31) was observed, which was significantly lower compared to eyes without corneal perforation 73.9% (34/46) with a p-value of 0.008.

Conclusions: Limbal dermoid was the most common indication for paediatric keratoplasty, and it exhibited a better graft survival rate compared to other pathologies. A one-year graft survival rate varies among different indications of keratoplasty. Perforated cornea has a lower graft survival rate compared to non-perforated corneal pathology.

KEYWORDS:
Paediatric keratoplasty; cornea, corneal graft; graft surviva;, paediatric corneal blindness

INTRODUCTION

Corneal blindness is one of the most common avoidable causes of childhood blindness globally.[1] Multiple factors can contribute to corneal opacity in the paediatric population, necessitating corneal transplantation. These causes can be broadly categorised into congenital corneal opacity, acquired traumatic corneal opacity, and acquired non-traumatic corneal opacity.[2]

In developing countries, the primary indications for paediatric keratoplasty are often acquired non-traumatic corneal opacity, including infective keratitis, corneal ulcers with perforation, and post-infectious keratitis with corneo-iridic scars.[2,3] Conversely, in developed countries, congenital corneal opacity and keratoconus are the predominant reasons for penetrating keratoplasty in paediatric patients.[4–6]

Paediatric keratoplasty poses unique challenges due to factors such as small palpebral fissures, low scleral rigidity, high vitreous pressure, and a more crowded anterior segment, all of which require skilled surgical handling.[7] Postoperatively, these procedures are associated with significant inflammation, a high incidence of secondary glaucoma, and an elevated risk of graft failure.[2] Furthermore, graft rejection in paediatric patients often occurs more rapidly and is less responsive to treatment.[7]

The existing literature on the aetiology of corneal pathologies, clinical outcomes, and graft survival rates of paediatric keratoplasty in Malaysia is limited to the experience of a single centre.[3] Therefore, this study analysed the indications and outcomes of paediatric corneal transplantation performed at a single centre in a developing country over a 15-year period.

MATERIALS AND METHODS

This retrospective study was conducted at Hospital Kuala Lumpur in adherence to the tenets of the Declaration of Helsinki, with ethics approval obtained from the local

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institutional review board (Medical Research and Ethics Committee, Ministry of Health; NMRR ID-23-03571-HXW). Paediatric patients (aged 12 years or younger) with corneal pathologies who underwent corneal transplantation between January 2008 and December 2022 were included. Patient identities were retrieved from the corneal transplant logbook maintained by the Department of Ophthalmology at Hospital Kuala Lumpur.

All corneal transplantation surgeries were performed under general anaesthesia by two corneal consultants at Hospital Kuala Lumpur. Some cases involved collaboration with paediatric ophthalmologists and oculoplastic surgeons. The surgical techniques employed included penetrating keratoplasty and anterior lamellar keratoplasty. Indications for penetrating keratoplasty included diseases that affected the full thickness of the cornea. In contrast, patients with pathology limited to the anterior cornea were indicated for anterior lamellar keratoplasty. The standard microsurgical technique was used for all cases that underwent penetrating keratoplasty.

The anterior lamellar keratoplasty technique was described as follows: Partial-thickness trephination of the lesion was performed using a trephine, followed by lamellar delineation starting at the corneal site using a crescent knife. Lamellar delineation was repeated as needed to dissect until most of the opacity was excised and the remaining deep cornea was relatively clear. Cautery was applied when necessary. A corneoscleral graft of similar thickness was trephined from a whole globe donor. Grafts were sized the same as the lesion, with an additional oversize of 0.25–0.5 mm. The corneoscleral graft was then dissected in a lamellar fashion using a crescent knife. The graft was secured to the host cornea and sclera using interrupted 10-0 nylon sutures. Most corneal grafts were imported from the United States, with a minority sourced from local donors.

Basic demographic data were collected. Factors of interest included age, diagnosis, surgical indications (congenital corneal opacity, acquired non-traumatic corneal opacity, and acquired traumatic corneal opacity), type of surgery, complications, graft failure, and survival periods.

The patient was followed up on postoperative day 1, 1 week, 1 month, 6 months, and 1 year. More frequent visits may be needed depending on the patient's condition. Patients who did not attend their one-year follow-up for any reason were excluded from the one-year graft survival data analysis. Graft failure was defined as the irreversible loss of central graft clarity due to any cause, rendering the graft incompatible with good visual function. Data were analysed to determine the one-year graft survival rate.

Statistical analysis

All the data analysis was analysed using SPSS version 25. Descriptive data was conducted to describe the demographics of the population. Categorical data was expressed in frequency and percentage, numerical data was expressed in terms of mean and standard deviation (if normally distributed), and median with interquartile range (if abnormally distributed). For inferential analysis, all the categorical data was analysed with the chi-square test, while numerical data was analysed with the independent t-test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 95 patients underwent 100 corneal transplantations, with two patients receiving bilateral keratoplasty and three repeated grafts performed in two patients. Demographic data of the patients as shown in Table I.

Among the 100 eyes, 44% underwent penetrating keratoplasty, and 56% underwent anterior lamellar keratoplasty. Indications for ALK included corneal scar, corneal haemangioma, cryptophthalmos, exposure keratopathy, ocular surface disease, neurotrophic keratopathy, and limbal dermoid. Indications for PK included Peters anomaly/anterior segment dysgenesis (ASD), bullous keratopathy, infective keratitis, and corneal perforation.

The mean donor size was 7.57 mm (range: 6–14.5 mm), and the mean recipient size was 7.07 mm (range: 5.5–13.5 mm). The indications for paediatric keratoplasty were categorised into 3 groups: congenital corneal opacity, acquired non-traumatic corneal opacity and acquired traumatic corneal opacity. These groups were further subdivided into specific aetiologies as shown in Table II. Some of the photographs taken before and after paediatric keratoplasty as shown in Figure 1.

At one year, 77 eyes (77%) were compliant with follow-up. The overall one-year graft survival rate was 54.5%. Survival rates by indication were 64% for congenital corneal opacity, 35.3% for acquired non-traumatic corneal opacity, and 100% for acquired traumatic corneal opacity. One-year graft survival rate segregated by specific aetiology was illustrated in Figure 2.

Eyes with limbal dermoid demonstrated the highest one-year graft survival rate, with a p-value of 0.004. However, eyes with corneal perforations had a significantly lower survival rate (25.8%) compared to those without perforation (73.9%). Further analysis of various variables in relation to 1-year graft survival were shown in Table III.

Postoperative complications included infective keratitis (4%), wound dehiscence (4%), and graft melting (3%). All cases of wound dehiscence were associated with postoperative ocular trauma, leading to graft failure and, in two cases, phthisis bulbi.

DISCUSSION

This retrospective study outlines the demographics, indications, and outcomes of paediatric corneal transplantation procedures performed at Hospital Kuala Lumpur, Malaysia, between January 2008 and December 2022. As a tertiary referral centre, our facility specialises in paediatric ophthalmology services in Malaysia, offering a comprehensive overview of Southeast Asian corneal diseases within a predominantly urban population.

Table I: Demographic data of patients underwent paediatric keratoplasty (n=95)

	Frequency, n (%)
Gender	
Male	48 (50.5)
Female	47 (49.5)
Age (years old)	
<1	26 (27.4)
1-3	16 16.4)
4-6	29 (30.5)
7-9	20 (21.1)
10-12	4 (4.2)
Race	
Malay	62 (65.3)
Chinese	13 (13.7)
Indian	4 (4.2)
Iban-Kadazan	12 (12.6)
Others	4 (4.2)

Table II: Indications for paediatric keratoplasty (n=100)

Indications	No. of eyes (n)	Percentage (%)
Congenital	75	75
Corneal haemangioma	1	1
Corneal scar	1	1
Cryptophthalmos	2	2
Congenital glaucoma	4	4
Anterior segment dysgenesis + Peter's anomaly (ASD)	22	22
Limbal dermoid	45	45
Acquired non-traumatic	23	23
Bullous keratopathy	2	2
Ocular surface disease	1	1
Neurotrophic keratopathy	3	3
Exposure keratopathy	3	3
Infective keratitis	14	14
Acquired Traumatic	2	2
Corneal scar	2	2

Table III: Variables associated with 1-year graft survival rate

Variables	1-year graft survival (n, %)	χ^{2*}	p-value
Type of pathologies			
Limbal dermoid	26 (72.2%)	12.08	0.004
Other pathologies	16 (39%)		
Congenital corneal opacity	34 (58.6%)	1.574	0.210
Acquired non-traumatic corneal opacity	8 (42.1%)		
Non-perforated	34 (73.9%)	8.95	0.003
Perforated	8 (25.8%)		
Type of surgeries			
Lamellar keratoplasty	31 (66%)	6.337	0.012
Penetrating keratoplasty	11 (36.7%)		

*Chi-square test

The indications for paediatric keratoplasty vary based on regional disparities in economic and sanitary conditions. In developing countries like India, non-traumatic acquired corneal opacity resulting from infective keratitis is the primary indication for paediatric corneal transplantation.[8] In contrast, countries such as Saudi Arabia, Iran, and Pakistan report a higher prevalence of congenital glaucoma and congenital hereditary endothelial dystrophy, likely due to a greater incidence of consanguinity.[9–11] In developed countries like the United States and China, congenital corneal opacity is the leading indication for paediatric keratoplasty.[4,6]

In our study, Hospital Kuala Lumpur received referrals for paediatric corneal diseases from across Malaysia. Congenital corneal opacity accounted for 75% of cases, with limbal dermoid identified as the most common indication for paediatric keratoplasty. These results differ from another Malaysian study conducted in a single-state population of a suburban area, where infective keratitis was the leading indication.[3] This variation may reflect differences in parental awareness and access to healthcare within the country. Urban parents, who tend to be more attentive to their children's needs, are more likely to seek medical attention promptly. They often adopt a more protective approach to

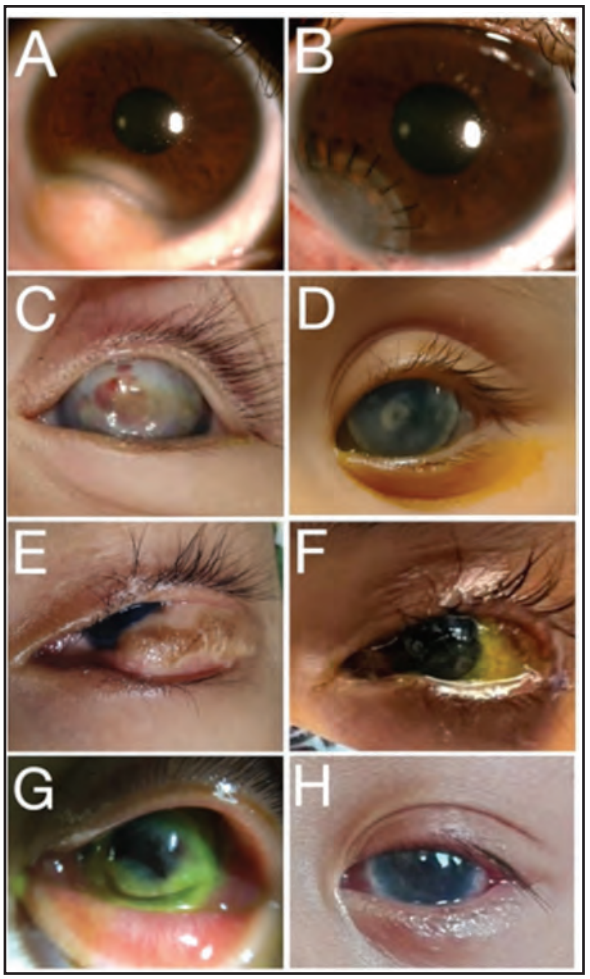

Fig. 1: A & B) Limbal dermoid before and after lamellar keratoplasty. C&D Peter's anomaly before and after penetrating keratoplasty. E&F Cryptophthalmos before and after lamellar keratoplasty, combined with lid and fornix reconstruction, represents a collaborative effort. G&H Infective keratitis with perforation before and after penetrating keratoplasty

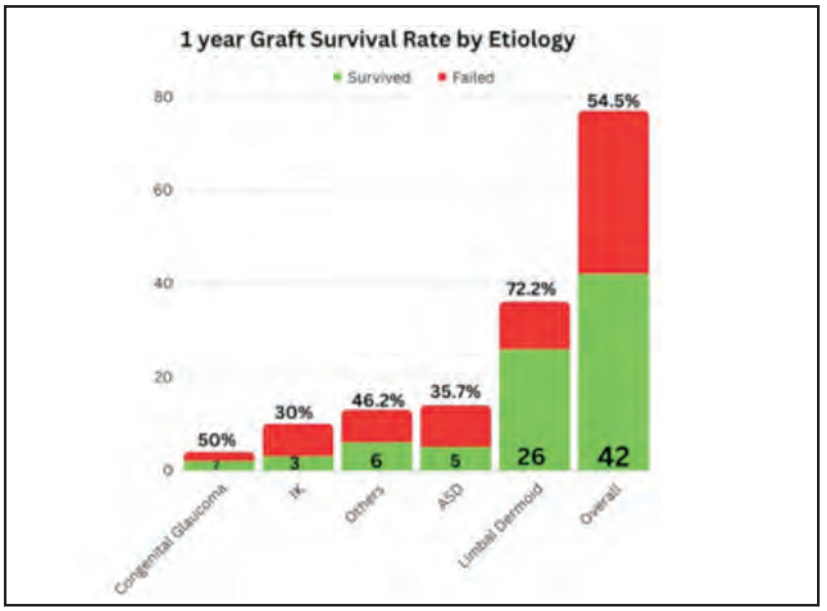

Fig. 2: Bar chart shows 1-year graft survival rate segregated by aetiology. IK: Infective keratitis; ASD: Anterior Segment Dysgenesis

parenting compared to parents in suburban areas, where children typically spend more time outdoors. Increased outdoor activities in suburban settings may expose children to a higher risk of eye injuries, which can potentially lead to infective keratitis.

Indications for paediatric keratoplasty also vary by age. In studies including patients up to 18 years old, acquired causes and keratoconus are the primary indications for paediatric keratoplasty.[12,13] However, studies focusing on younger patients (less than 12 years old) predominantly report congenital corneal pathologies as the main indication.[10] Our findings align with these reports, with 75% of our patients requiring corneal transplantation due to congenital corneal opacity or limbal dermoid.

One-year graft survival rates in countries where congenital corneal opacity is the primary indication for surgery range from 54% to 90.7%.[7,14] Similarly, our study observed a 54.5% survival rate for corneal grafts remaining clear after one year. No significant differences were noted between the congenital and acquired corneal opacity groups, consistent with previous studies.[6,7] However, limbal dermoid demonstrated the highest 1-year graft survival rate among all indications. Spierer et al. reported a 100% survival rate for limbal dermoid following lamellar keratoplasty.[15] Based on our findings, we anticipate favourable outcomes for patients with limbal dermoid.

Additionally, lamellar keratoplasty exhibited a higher 1-year graft survival rate compared to penetrating keratoplasty. Few studies compare both techniques directly.[5,16–18] Low et al. reported similar graft survival outcomes for both procedures,[18] but differences in patient age and surgical settings may explain variability in outcomes. For example, the Singapore study included patients up to 16 years old, whereas our analysis focused on children 12 years old and younger. Furthermore, all paediatric keratoplasty procedures in Singapore were conducted by a single surgeon, whereas two corneal consultants performed the surgeries at our institution. These factors could potentially influence the outcomes. Buzzonetti et al.[5] reported that deep anterior lamellar keratoplasty yielded better graft survival compared to penetrating keratoplasty, findings that align with our results.[5] Achieving good host-graft apposition in lamellar keratoplasty may provide an advantage in the paediatric population, given their active immune systems.

Interestingly, our study revealed that corneal perforations significantly reduced the 1-year graft survival rate compared to non-perforated corneal pathologies. To our knowledge, no prior studies have investigated this association in paediatric patients, underscoring the novelty of our findings. It is plausible that corneal perforations increase tissue damage and activate inflammatory cascades, thereby elevating the risk of graft rejection and failure.

Postoperative complications, including graft rejection, infective keratitis, wound dehiscence, graft melting, phthisis bulbi, and endophthalmitis, are commonly reported in prior studies.[2,3,18] The active nature of paediatric patients often results in postoperative ocular trauma, leading to complications such as wound dehiscence and graft failure, as observed in our cohort. Parent counseling regarding postoperative care and monitoring is crucial. Early detection of abnormalities by parents can facilitate timely intervention and prevent complications. Despite these efforts, postoperative complications remain a significant challenge, often necessitating regrafting procedures.

This retrospective study's primary limitations include a relatively small sample size and variable follow-up periods. However, such constraints are common in studies on paediatric keratoplasty due to the rarity of these procedures. Additionally, corneal clarity was the primary outcome measure, as assessing visual acuity in younger paediatric patients presents unique challenges. Nevertheless, this study provides valuable insights into the indications, risk factors, and 1-year graft outcomes of paediatric keratoplasty in Southeast Asian eyes, with a predominantly Malay representation.

CONCLUSION

Limbal dermoid emerged as the most prevalent indication for paediatric keratoplasty in Malaysia, demonstrating a superior graft survival rate compared to other pathologies. Our study shows that 1-year graft survival rate varies among different indications. Additionally, lamellar keratoplasty was associated with a higher 1-year graft survival rate in comparison to penetrating keratoplasty. Corneas with perforations exhibited a lower graft survival rate than non-perforated corneal pathologies. Enhanced comprehension and management of paediatric keratoplasty may aid in patient selection and further enhance graft survival outcomes.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Characteristics and outcomes of out-of-hospital cardiac arrest cases responded by emergency medical services across three states in Malaysia

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ABSTRACT

Introduction: Out-of-hospital cardiac arrest (OHCA) is globally a critical, time-sensitive emergency with varying outcomes. In Asia, the Pan Asian Resuscitation Outcome Study reported survival rates between 0.5% to 8.5%. We aim to describe the characteristics and outcomes of OHCA cases responded to by Emergency Medical Services (EMS) across several cities in Sarawak, Penang and Klang Valley in Malaysia.

Materials and Methods: This retrospective observational study analysed EMS data from Sarawak, Penang and Klang Valley from 2010 to 2019. All OHCA cases where EMS performed cardiopulmonary resuscitation (CPR) were included, regardless of age or aetiology. The primary outcome was survival to hospital admission with the secondary outcome a return of spontaneous circulation (ROSC) prior to Emergency Department arrival.

Results: A total of 2,435 OHCA cases were analysed. Median patient age was 58 years, 70% of them are male with 63% had underlying medical conditions, with hypertension being the most common. Out of all cases, 71% of arrests occurred at home, 60% witnessed. Median time from arrest to 999 call was 20 minutes, median time for ambulance arrival thereafter is 17 minutes. Bystander CPR rate was 38%, bystander Automated External Defibrillator (AED) use 1.5-2.6%. Detection of shockable rhythm on first analysis by EMS was 3.9 to 7.7%. Overall survival to admission rate was 4.76%. ROSC rate before Emergency Department arrival was 2.8%. Survival to admission among bystander-witnessed arrests with shockable rhythm was 14.7%.

Conclusion: Survival to admission rates for OHCA patients in the studied Malaysian regions (1.3-6.7%) are lower compared to some Asian countries. Areas for improvement include reducing time from arrest to 999 calls, decreasing time to EMS arrival, and increasing bystander CPR and AED use rates. Implementing the Utstein ten-step implementation strategy, focusing on community-based interventions and improving EMS response, could potentially enhance survival rates in Malaysia.

KEYWORDS:
Out-of-hospital cardiac arrest, Emergency Medical Services, Cardiopulmonary resuscitation, survival rates, Utstein reporting

INTRODUCTION

Out of Hospital Cardiac Arrest (OHCA) is a time-sensitive, life-threatening emergency.[1] OHCA is defined as cessation of cardiac mechanical activity associated with absence of circulation outside of hospital setting.[2] Global incidence of OHCA average about 55 adults per 100,000 population per year.[1] Outcomes and survival of OHCA differ between countries.[3,4] There are limited reports reflecting lower middle and upper middle-income countries with developing EMS system.[3] In 2015, the Pan Asian Resuscitation Outcome Study (PAROS) reported survival rate across participating countries in Asia between 0.5% to 8.5%.[3] The report also shows that within the same country, the survival rate varies.[3] Malaysia, as a collaborator in PAROS, has survival rate of less than 10%.[3]

Worldwide there has been studies that shows a differing range of OHCA survival rates even within the same country.[3,5] The Utstein Formula for Survival describes that survival from OHCA is dependent on three interacting factors: science, education and local implementation of the chain of survival.[6] Modifiable factors related to OHCA survival are patient age, comorbidity, initial cardiac rhythm, witness status, bystander cardiopulmonary resuscitation (CPR), bystander defibrillation, emergency medical service (EMS) response time and interventions and in-hospital interventions.[7-9]

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EMS system in Malaysia is under the Emergency Medicine and Trauma Services.[10] The system is predominantly hospital-based provider utilising Assistant Medical Officers (AMO) as the core response personnel. AMO are authorised to provide manual defibrillation, provision of advanced airway intervention and administration of resuscitation medications when managing OHCA. The training of Advanced Life Support interventions for AMO in OHCA adheres to the National Committee on Resuscitation Training Ministry of Health.[11]

At present there is no National Cardiac Arrest Registry for Malaysia, however there is an interest to collect EMS data on OHCA by individual hospitals voluntarily. Malaysia is part of the original PAROS committee, which was established since 2009, with the registry data collection beginning in 2010.[12] Adapting the PAROS registry database collection, our study aims to provide a description of patients, public and EMS resuscitation efforts for cases of OHCA across 3 states in Malaysia. Understanding the demography and response factors related to OHCA intervention will allow policy makers and service operators to prioritise the logistics and finance required to improve survival rate within their own community.[13] It also prevents generalisation of intervention because each service operation may differ in terms of population demography, geographical challenges and disease pattern.

MATERIALS AND METHODS

This is a retrospective observational study utilising EMS data from participating centres around Sarawak, Penang and Klang Valley. Ethics approval was obtained from the national Medical Research Ethics Committee NMRR-11-187-8792. Malaysia is part of the original PAROS committee which was established since 2009 wherein the registry database was inaugurated in 2010 for data collection. For this study our team used a common data collection form adapted from the PAROS registry.[12] For reporting purposes, centres are clustered into 3 states Penang, Klang Valley and Sarawak. Data from 2010 until 2019 were used for analysis.

The study included data of all OHCA cases adult, newborn or paediatric age group regardless of aetiology with cardiopulmonary resuscitation performed by EMS. The primary outcome measured was survival to hospital admission. Survival to hospital admission is defined as patients with return of spontaneous circulation (ROSC) that has been reviewed and planned for admission to definitive care. The secondary outcome measured was any ROSC reported by EMS prior to Emergency Department arrival. We did not measure 30-day survival rate as it is a summation of both EMS and in-hospital intervention, which was not the focus of our study.

Core data variables are clustered into several components such as patient demography, and bystander intervention. Patient age and EMS response times are summarised using mean standard deviation and median quartiles. Categorical data of EMS response and intervention, prehospital outcome, and outcome of patients at the Emergency Department are summarised compiled using frequency and percentages. All cases with missing variable data are excluded from the analysis. Incidence rates and outcome of OHCA are reported tabulated in frequencies and percentage according to state for comparison. Data analysis utilised SPSS Statistical software version 29.

RESULTS

A total of 2435 patients from 6 hospital-based EMS were included in the study. Table I shows the characteristics of patient between the 3 states from January 2010 till December 2019. The majority of patients age group was between 40 to 60 years, of which 0.5% of patients were less than 12 years of age. Median age of patients was 58 years old (mean 56, Standard deviation ± 18.31) whereby 70% of patients were male. The percentage of patients had underlying medical illnesses with hypertension as the most common comorbidity followed by diabetes mellitus was 63%, wherein 9% of patients had a combination of hypertension, diabetes mellitus and ischaemic heart disease.

Table II describes the cardiac arrest characteristics by states. A total of 71% of the arrest occurred at home residences compared to 10% that occurred in public or commercial buildings. Further, 60% of arrest were witnessed by either bystanders or EMS responders (53% and 7% respectively). Only 2% of arrest occurred during EMS care within the ambulance during transportation. The median time taken from arrest to 999 call was 20 minutes (mean 34 minutes, standard deviation ± 46 minutes). Klang Valley region had the longest median time from arrest to 999 call of 28 minutes (mean 39 minutes, standard deviation ± 47 minutes). Median time from 999 call to EMS arrival was 17 minutes (mean 18 minutes, standard deviation ± 11 minutes).

Table III describes the prehospital intervention by either bystander or EMS according to region. The overall bystander CPR rate is 38% with Klang Valley having only 35.5% bystander CPR. With regards to EMS intervention, Penang had a higher rate for defibrillation, use of mechanical CPR device, administration of adrenaline and advanced airway insertion (11.1%, 30.6%, and 65.8% respectively). Advanced airway intervention was widely used in Penang, with 70.3% of their patients had Laryngeal Mask Airway (LMA) applied during CPR. Sarawak performed more endotracheal intubation during CPR compared to the rest (31.3%). The primary outcome of survival to admission was 4.76% with Penang achieving 6.65%. Rate of ROSC prior to arrival to Emergency Department was 2.8% with Penang having a rate of 3.7%.

Figure 1 shows the summary of Utstein reporting parameters for Malaysia. The overall survival to admission rate for witnessed arrest with EMS cardiopulmonary resuscitation intervention and shockable rhythm analysis was 14.7%. There are 25 (2.5%) OHCA patients with initial rhythm that is non-shockable or asystole survived till admission.

DISCUSSION

Our study is the first to compare OHCA outcomes between states in Malaysia. Since Malaysia has not yet set up a

Table I: Patient demographics for all cases by states in Malaysia

Characteristic	Sarawak	Penang	Klang Valley
Total centres	2	1	3
Total population	77	767	1591
Age			
Mean	56	58	56
Std deviation	18.5	17.9	18.5
IQR:			
25	45	48	46
50	60	60	58
75	68	71	68
Gender (n, %)			
Male	60 (77.9)	557 (72.6)	1090 (68.5)
Female	17 (22.1)	210 (27.4)	500 (31.4)
Missing data			1 (0.1)
Past medical history (n, %)			
No known medical illness	8 (10.4)	59 (7.7)	391 (24.6)
Unknown if medical illness is present	20 (26.0)	249 (32.5)	184 (11.6)
Medical illness present	49 (63.6)	459 (59.8)	1016 (63.9)
Type of medical illness, when present (n, %)			
Heart disease, Hypertension, Diabetes (all present)	3 (4)	65 (8.5)	146 (9.2)
Heart disease	12 (16.9)	180 (23.5)	353 (22.2)
Diabetes	16 (20.8)	218 (28.4)	486 (30.5
Cancer	4 (5.2)	29 (3.8)	88 (5.5%)
Hypertension	28 (36.4)	235 (30.6)	549 (34.5)
Renal	3 (3.9)	59 (7.7)	122 (7.7)
Respiratory	4 (5.2)	44 (5.7)	127 (8.0)
Hyperlipidaemia	5 (6.5)	18 (2.3)	27 (1.7)
Stroke	4 (5.2)	34 (4.4)	79 (5.0)

Table II: OHCA characteristics for all cases by states in Malaysia

Characteristic	Sarawak	Penang	Klang Valley
Location type (n, %)			
Missing data			2 (0.13)
Home residence	43 (55.8)	488 (63.6)	1208 (75.9)
Healthcare facility	6 (7.7)	37 (4.8)	69 (4.3)
Public/commercial building	11 (14.3)	101 (13.2)	131 (8.2)
Nursing home	3 (3.9)	35 (4. 6)	15 (0.9)
Street/highway	58 (7.6)	69 (4.3)	134 (5.5)
Industrial place	1 (1.3)	6 (0.8)	13 (0.8)
Transport centre	1 (1.3)	2 (0.3)	15 (0.9)
Place of recreation	0 (0.0)	14 (1.8)	26 (1.6)
In EMS/private ambulance	4 (5.2)	20 (2.6)	15 (0.9)
Others	1 (1.3)	6 (0.8)	28 (1.76)
Arrest witnessed by (n, %)			
Missing data			1 (0.1)
Not witnessed	28 (36.4)	324 (42.2	630 (39.6)
Bystander	38 (49.4	355 (46.3%)	881 (55.4)
EMS	11 (14.3%)	88 (11.5)	79 (5.0)
Time from arrest to 999 call (minutes)			
Mean	39.9	19.8	38.7
Standard deviation	65.6	36.7	46.5
IQR:			
25	5	6	10
50	14	11	28
75	49	21	49.3
First arrest rhythm (n, %)			
Missing data			
VT/VF/unknown shockable	4 (5.2)	59 (7.7)	62 (3.9)
Unknown unshockable	1 (1.3)	102 (13.3)	176 (11.1)
Asystole	43 (55.8)	476 (62.1)	1196 (75.2)
Pulseless electrical activity	16 (20.8)	39 (5.1)	32 (2.0)
Unknown	13 (16.9)	91 (11.9)	125 (7.9)

Table III: Prehospital care interventions and outcomes for all out-of-hospital cardiac arrest by states in Malaysia

Characteristic	Sarawak	Penang	Klang Valley
Time 999 call to EMS arrival (minutes)			
Mean	19	15.4	20.5
Std deviation	9.2	8.9	11.8
IQR:			
25	12	10	14
50	17	14	19
75	23	19	25
Bystander intervention (n, %)			
Bystander Cardiopulmonary Resuscitation (CPR)	32 (41.6)	321 (41.9)	564 (35.5)
Bystander using Automated External Defibrillation (AED) device	2 (2.6)	19 (2.5)	23 (1.5)
EMS responder intervention (n, %)			
Prehospital defibrillation	6 (7.8)	85 (11.1)	89 (5.6)
Prehospital adrenaline	30 (39)	504 (65.7)	401 (25.2)
Prehospital mechanical CPR device	1 (1.3)	235 (30.6)	87 (5.5)
Prehospital advanced airway	31 (40.3)	620 (80.8)	508 (31.9)
OHCA outcomes (n, %)			
ROSC at scene	6 (7.8)	28 (3.7)	34 (2.1)
Arrive to ED in ROSC	4 (5.2)	23 (3. 0)	22 (1.4)
Survived to admission	1 (1.3)	51 (6.7)	64 (4.0)
Survived till discharge	0 (0.0)	5 (0.7)	15 (0.9)

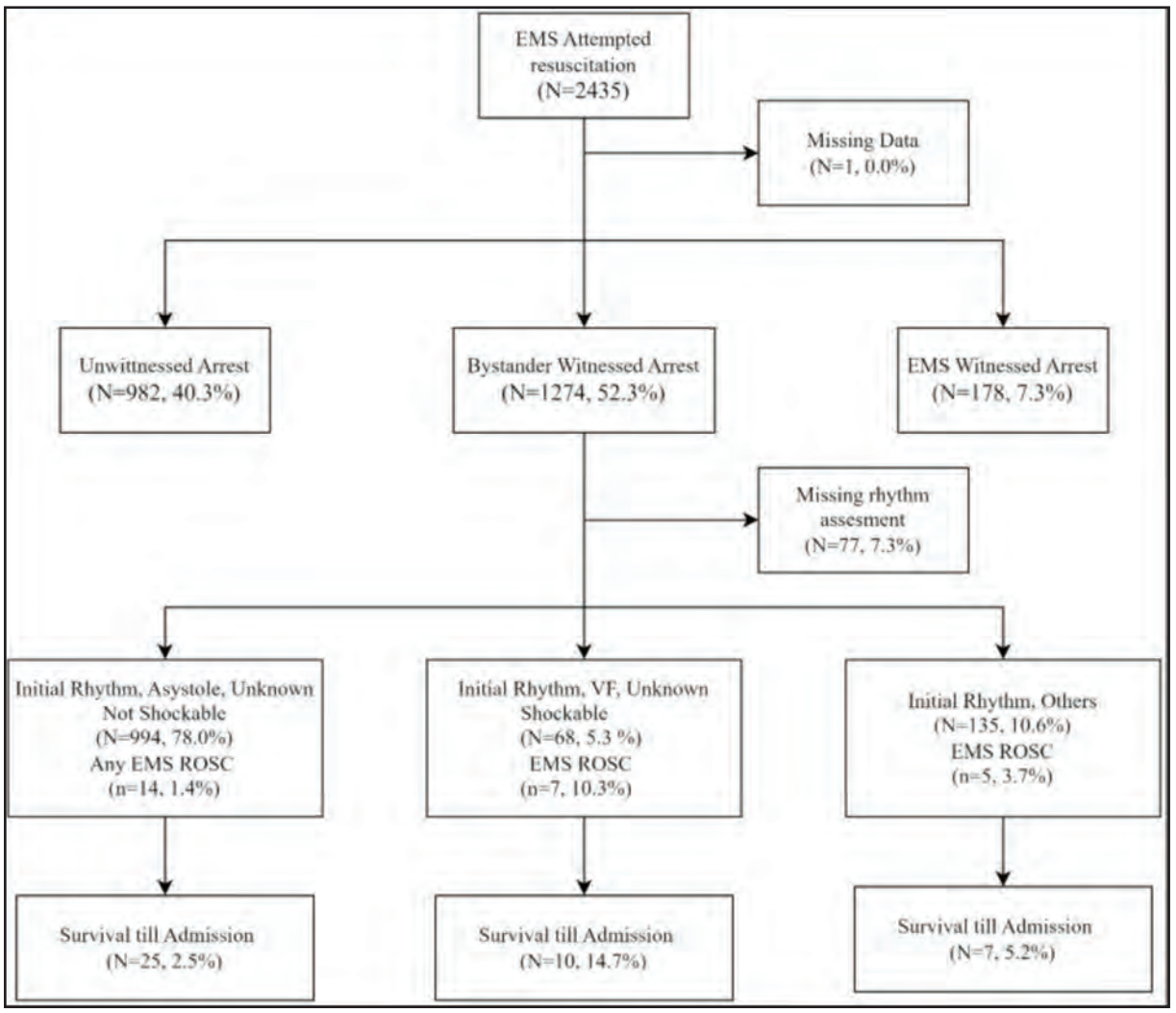

Fig. 1: Utstein survival reporting chart for overall OHCA outcome in Malaysia

National Cardiac Arrest Registry, EMS data collection for hospitals in each state are voluntary. Our data capture the EMS in major cities such as Georgetown, Kuala Lumpur, Petaling Jaya, Ampang, Kuching and Miri. Therefore, the findings reflect urban EMS systems. Among the three states; centres from Sarawak have the lowest population density with 48.3 to 754 per square kilometre. Centres from Penang and Klang Valley have higher population density of 2500 to 3000 per square kilometre.[14] In 2015, the PAROS investigators published their first report analysing OHCA in 7 countries across Asia.[3] Data from Malaysia utilised in their analysis at that time was only 389 for the period of 2010 until 2012. Our study extended the data collection period until 2019 with more centres contributing data. In total we analysed 2435 OHCA cases with CPR initiated or continued by EMS.

Our study shows that majority of OHCA occur among patients who are still within the working age group. Our mean age of 56 to 58 years is younger compared to Singapore of 66 years and Thailand of 67 years.[15,16] The PAROS team reported much younger age of OHCA victims in United Arab Emirates-Dubai which is 49 years old. It was attributed to younger migrant population within the country.[3] The same observation is not seen in our study. Similarities across the region of Asia, majority of victims are male and majority of OHCA occurred at home residence (56 to 76%).[3] The overall bystander CPR rate of 36 to 42% seen in our study is better than previously reported by PAROS at 16.5 to 21%.[17] 999 Dispatchers in Malaysia have been providing Dispatch Assisted CPR (DA-CPR) instructions since 2011. Compared to other Asian countries providing DA-CPR intervention, our rate of bystander CPR is lower compared to Singapore (50.4%) and Korea (47.3%).[17] Both Korea and Singapore have implemented the Utstein Ten-Step Implementation Strategy (UTIS) which advocates community bundle programs of DA-CPR and school CPR.[18,19] Based on our findings most witnessed OHCA occurs at home. We need to start educating and at least adopt a school CPR program in secondary schools. This initiative potentially leads to one rescuer for each household. This, together with DA-CPR will improve our bystander CPR rate. This is a critical factor to consider in the planning of Public Access AED programs.

Our bystander rate of using Automated External Defibrillator (AED) is between 1.5 to 2.6%. During the study period, Malaysia has yet to initiate a nationwide Public Access Defibrillator (PAD) program. Only in the state of Penang, since 2016 PAD program was initiated and led by the state government. It is only in 2022, that the Minister of Health proposed to make AED compulsory in all government buildings.[20] Since the majority of OHCA occurs within the home residence, it is also imperative that Public AED program include residential areas such as condominiums and public housing. Placement of AEDs within public access on its own will not lead to improved utilisation. As mentioned by Chew et. al reducing fear regarding its utilisation and promoting societal expectation change that use of an AED is an expected intervention when someone was to collapse is also critical.[21]

The median time from arrest to 999 calls ranges between 11 to 28 minutes (Table II). This has not much improved compared to 19 minutes reported by PAROS.[3] After 10 years initiation of Malaysian Emergency Response System 999 (MERS999) we have yet to targeted achieved 2 to 3 minutes time from arrest to 999 calls as seen in Japan, Korea and Singapore.[3] Median time from 999 call to EMS arrival ranges between 17 to 19 minutes. This may reflect our hospital-based EMS where the ambulance is stationed within hospitals rather than closer to community. One of the modifiable factors to improve survival in OHCA is to have an EMS arrival time of less than 8 minutes.[8] Having a faster EMS arrival time improves the chances of shockable rhythm or Ventricular Fibrillation (VF) on first rhythm analysis.[22] Our study showed detection of shockable rhythm or VF on first rhythm analysis by EMS is between 3.9 to 7.7%. This finding has not improved from the PAROS report.[3] Therefore, it is important for Malaysia especially in densely populated areas to improve its ambulance arrival time.

The overall survival to admission among OHCA patients was between 1.3 to 6.7%. This is lower compared to previous report of 8% by the PAROS investigators.[3] Penang has the highest rate of survival to admission at 6.7% compared to Sarawak (1.3%) and Klang Valley (4.0%). This may be due to a faster median time from call to ambulance arrival, higher bystander CPR rate and higher prehospital defibrillation rate. Penang also has higher rate of mechanical CPR device being used. The benefit of mechanical CPR device during transport is its ability to provide a constant high-quality compression in a moving ambulance.[23] Utilising the Utstein template of reporting, we found that overall survival to admission among bystander witnessed arrest and presence of shockable rhythm on first rhythm analysis was 14.7%. Our survival to admission rate is lower compared to Thailand of 40.8%.[24]

Our analysis shows the deficit within our public awareness and EMS system in managing OHCA. The Utstein Formula for Survival describes that survival from OHCA is dependent on three interacting factors: science, education and local implementation of the chain of survival.[6] Adopting the UTIS recommendation for Malaysia especially on the community-based intervention may improve the overall survival as seen in countries that has begun to implement the strategy.[8,13,18] Besides improving our EMS response time; our community must be educated on the importance of their action to start CPR and early defibrillation whenever an AED is available nearby in OHCA situation. We must also, realize the aspirations of the then Health Minister to make AED compulsory in all government buildings.[20]

Our study is limited by the number of participating sites contributing data. Data are collected voluntarily, and it does not reflect total cases responded for each state. Since the sites are all urban centres, our study also does not reflect non-urban communities. Another limitation of the study is that our team also could not differentiate between traumatic arrest and non-traumatic arrest. Many of the EMS data obtained did not specify the probable cause of arrest as either traumatic arrest, or presumed cardiac arrest, or respiratory arrest or unknown. The majority of the sites classify the arrest as unknown. Future research needs to differentiate between the two as the intervention provided by EMS is different. Based on our study, we recommend Malaysia to set up a National Out of Hospital Cardiac Arrest Registry for robust data collection and provide better insight to interventions

that can improve survival rate. Future research is required to investigate individual areas such as type of arrest, age category and location category.

CONCLUSION

Our study found that survival to admission rates among OHCA patients in 3 regions of Malaysia are between 1.3 to 6.7%. These survival rates are low and could be improved if Malaysia adopts the UTIS bundle program aimed at improving modifiable OHCA survival factors such as bystander CPR and defibrillation. This also includes increasing resources towards further efforts at improving EMS arrival time.

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Exploring psychosocial needs of young women with breast cancer in a country with crisis: a mixed-methods study

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ABSTRACT

Introduction: Previous research conducted in politically stable countries showed that the diagnosis and treatment of breast cancer among young women can be very distressing and devastating and may result in a lot of unmet psychosocial needs affecting their quality of life. This study aimed to address the psychosocial needs of young women with breast cancer in war-torn Syria.

Materials and Methods: A mixed-methods explanatory sequential design was employed in this study. Initially, a quantitative survey was conducted for 3 months from May to July 2022 on 167 young women using the Psychological Needs Inventory to identify their psychosocial needs. Secondly, a qualitative, semi-structured interview was conducted for 6 months from July to December 2022 with 11 participants to explore the challenges faced in meeting these needs.

Results: The quantitative results showed that three items, "Help with financial matters", "Advice about food and diet", and "Help with transport", were identified as significant unmet psychosocial needs. All three items fall within the category of practical needs. The qualitative results identified five themes: (1) challenges of adequate information needs with five subthemes (inadequate communication with the health professionals, lack of educational programs and awareness campaigns, inadequate number of nurses, need for nutritionists, and effects of unmet informational needs); (2) psychological challenges with five subthemes (uncertainty of the future, fear concerning the children, fear of death, treatment-related effects and the loss of a woman's identity, and inadequate psychosocial care); (3) financial challenges with 2 subthemes (treatment not available and expensive, low incomes and high cost of living); (4) social influences with 2 subthemes (society's view and stigma, lack of marriage choices); and (5) environmental stressors with 2 subthemes (stressful hospital environment and situational factors).

Conclusion: These psychosocial needs identified were found to align with Maslow's hierarchy of needs, underscoring a cascading effect of the Syrian crisis across various dimensions of well-being. Young breast cancer women living in countries with crises have high levels of unmet psychosocial needs.

KEYWORDS:
Young women, breast cancer, crisis, Maslow hierarchy of needs, and psychosocial needs

INTRODUCTION

Breast cancer is a significant public health problem in low and middle-income countries.[1,2] Although it was previously known as a disease of older women; its incidence has significantly increased among younger women in recent decades.[3,4] Since 2011, the crisis in Syria has deeply impacted the lives of its citizens. The last statistics available on breast cancer were published in 2009 by the Syrian National Cancer Registry, but no further report has been published since then due to the constraints on the registry after the start of the country crisis.[5,6] However, the number of breast cancer cases in Syria was likely to keep increasing. For example, according to data from the Al-Bairouni and Tishreen University Hospitals, breast cancer accounted for 24% and 23%, respectively, of all cancer cases in 2020.[7]

Breast cancer can significantly impact the psychosocial needs of young women with this disease. Previous studies revealed that young women with breast cancer can have significant unmet information needs,[8-10] psychological needs,[4,10,11] social needs,[4,10,12] and practical needs.[13,14] These psychosocial needs were shown to be associated with poor adjustment to the disease process, poor quality of life, and increased healthcare utilization and costs.[8,15-17]

However, most of these past studies on psychosocial needs came from politically stable countries. To the best of our knowledge, studies that addressed the psychosocial needs of young women with breast cancer in countries in war crisis are rare. Therefore, it is imperative to identify the psychosocial needs (and the extent to which these needs are unmet) of young women diagnosed with breast cancer through the lens of a country in crisis, such as Syria.

MATERIALS AND METHODS

Overall study design

This study adopted a two-phase mixed-methods explanatory sequential design to explore the psychosocial needs of young women with breast cancer in Syria. The first phase was a self-administered cross-sectional quantitative survey of 167 young women with breast cancer from Tishreen University

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Hospital in Latakia City, Syria, aimed to determine the types of psychosocial needs ranked according to importance or priority (conducted for 3 months from May to July 2022). The second phase was a semi-structured interview with 11 participants who had already completed the quantitative survey in Phase 1, with the aim to explore deeper into the challenges faced in meeting these needs (conducted for 6 months from July to December 2022). The ethical approval for conducting this study was obtained from the institutional medical ethics committee of University Malaysia Sarawak (No. FME/22/42); approval was also obtained from the Department of Oncology at Tishreen University Hospital. Informed consent was obtained from the participants who agreed to participate in the study.

Phase 1: The quantitative survey

Participants

A total of 167 young breast cancer women were conveniently recruited from Tishreen University Hospital in Latakia, Syria, which is the second most comprehensive Syrian oncology centre and receives cancer patients from many cities around Latakia. The sample size was estimated a priori using G*power software by employing an F test with an effect size set at 0.15, alpha level = 0.05, the power of study = 0.95 and number of predictors = 7 based on the theoretical framework of the validated Psychosocial Needs Inventory (PNI) used in this study. Based on these parameters, the initial estimate was 153 participants. To accommodate a potential lower response rate, an additional 10% was included, resulting in a final estimated sample size of 168 participants. The participants were included if they were aged between 18 and 50 years (defined as "young" in this study), had histologically proven breast cancer, and were proficient in the Arabic language. The rationale for the cut-off age of 50 years and younger in this study was based on previous studies that have consistently showed that women aged 50 years and below have greater psychological impact from breast cancer compared to women aged more than 50 years old.[18]

Procedures and materials

Data collection from participants in this phase was conducted using a structured questionnaire which included the socio-demographic data and the validated PNI instrument.[19] The PNI consists of 48 items under seven need categories: (1) interaction with health professionals (9 items); (2) information needs (5 items); (3) support networks (5 items); (4) identity needs (5 items); (5) emotional and spiritual needs (15 items); (6) practical needs (8 items); and (7) childcare needs (1 item). Every item in this questionnaire was ranked on its significance using a 5-point Likert scale ranging from 1 (not at all important) to 5 (very important) and the extent to which the participants were satisfied with acquiring support to meet their psychosocial needs on a 5-point Likert scale ranging from 1 (unsatisfied) to 5 (very satisfied). The PNI in this study was translated into Arabic language and the face validity was checked by an independent expert committee and the internal reliability ranged from 0.68 to 0.93. Statistical Package of the Social Scientists (SPSS), version 23.0 was used to generate the descriptive results of this study. With regards to the scoring of PNI, an item is defined as "significant" if that item is rated as "important" or "very important" by more than 50% of the participants of the 167 participants.[20] Similarly, an item is defined as "unmet" if it is rated as "unsatisfied" or "very unsatisfied" by more than 50% of the participants.[20]

Phase 2: Semi-structured qualitative interviews

Participants

The participants for this phase were conveniently recruited from the original sample in Phase 1. No other criteria were imposed in the recruitment of participants in this phase. The recruitment process was iteratively continued until data saturation was believed to have been achieved and no new findings or insights could be gleaned, which happened at the 11th participant in this study.

Procedures and materials

Data collection in this phase was conducted using semi-structured interviews arranged and performed by the first author who is a native Arabic speaker, from June to December 2022, each interview lasted for 45-60 minutes. The interviews were performed in the participants' homes to ensure privacy and comfort. The interview guide, informed by earlier quantitative findings in Phase 1 (where three items, i.e., "Help with financial matters", "Advice about food and diet", and "Help with transport", were identified as significant unmet psychosocial needs) as well as aimed at deeper exploration of other significant needs identified in that phase, with the following broad questions: (1) Can you describe the financial challenges you faced during your cancer treatment, and what kind of support or resources you think could help address these difficulties? (2) What kind of advice or guidance about food and diet have you received during your treatment, and what additional support do you feel is needed? (3) How has transportation affected your ability to attend treatments and appointments, and what changes or support would make this easier for you? (4) How have the psychological and emotional challenges of cancer impacted your treatment journey? (5) How do you feel about your communication with the healthcare staff during your treatment? (6) In your opinion, how has the Syrian societal misconceptions stigmatized breast cancer patients? The last question was added as there may be specific local socio-cultural nuances that could have positively or negatively influenced the psychosocial needs of these patients in Syria. First developed in English, the interview guide was then translated into Arabic and pilot-tested for clarity before being used for the interviews.

Data analysis

Contents of the interviews were audio recorded, transcribed verbatim, and translated into English by the first author. Although back translation was not performed, the accuracy of the forward translation was checked by an independent Egyptian language teacher who is proficient in both Arabic and English languages. Thematic analysis was then performed using NVivo 10 software. For this analysis, open coding (or first level coding) was initially performed by the first and second authors through iterative readings and labelling of keywords and phrases from the transcripts. After the initial open coding, a second axial coding (or second level coding) was performed by re-analysing these open codes to look for common themes among them. Discrepancy between researchers were resolved with mutual discussions in order to reach a consensus. Trustworthiness and credibility were enhanced through member checking by the participants.

Table I: The socio-demographic and illness-related characteristics of the sample

Variables	Classifications	Frequency (%) N = 167
Marital status	Single	17 (10.20)
	Married	140 (83.80)
	Divorced	1 (0.60)
	Widow	9 (5.40)
Number of children	No children	29 (17.40)
	One child	18 (10.80)
	Two children	41 (24
	Three children	38 (22.80)
	More than 3 children	41 (24.60)
Monthly income (USD)	Less than $35	58 (34.7)
	$36-50	82 (49.1)
	$51-75	15 (9.00)
	$76-100	7 (4.2)
	>$100	5 (3.0)
Family history of breast cancer	Yes	50 (29.9)
	No	117 (70.1)
Place of residence	Inside Lattakia	46 (27.5)
	Outside Lattakia	121 (72.5)
Type of treatment approach	Conservative	28 (16.8
	Mastectomy	139 (83.2)

RESULTS

Results from Phase 1: The quantitative survey

The mean age of the 167 participants was 42.04 years old, with the youngest participant aged 27 years old and the oldest participant aged 50 years old. The other detailed socio-demographic characteristics of the participants of Phase 1 are described in Table I.

Table II describes a list of "significant psychosocial needs" and "unmet psychosocial needs" based on participant responses. Interestingly, a deeper analysis of the findings in Table II reveals an apparent inconsistency between the data for "significant psychosocial needs" and the data for "unmet psychosocial needs." Specifically, only three items, i.e., "Help with financial matters," "Advice about food and diet," and "Help with transport", were identified as both significant and unmet needs. Notably, these three items fall within the category of practical needs. However, for the majority of the other items, the median scores for unmet needs were conspicuously low relative to their significance, suggesting that these psychosocial needs were largely "met", rather than "unmet".

Results from Phase 2: Semi-structured qualitative interviews

In this phase, five major themes were identified from this qualitative analysis.

Theme 1: *Challenges of adequate information needs*

Subtheme 1: Inadequate communication with the health professionals

All participants in the study expressed dissatisfaction regarding their communication experiences with their oncologists. Notably, participants said that the oncologists were often too busy to discuss their concerns. For example, one participant said:

"Due to the large number of patients, overcrowding, and many commitments at the hospital, the doctor has at least 40 files per day." – R.

In addition, 5 out of 11 participants also considered the limited number of oncologists in the hospital a barrier to good communication. They attributed this limited number of oncologists to the effects of the Syrian crisis that forced many physicians to leave the country, as demonstrated by what was said by this participant:

"There are some doctors who left the country during the crisis have not come back yet. They are getting more appreciation and support abroad, so, they will not come back." – W

Subtheme 2: *Lack of educational programs and awareness campaigns*

All participants noted a critical shortage of cancer educational and awareness programs and emphasized the need for more of these initiatives to be conducted in Syria to enhance breast cancer awareness and self-care knowledge among women. As one participant said:

"I feel that there is a great need for educational programs on television, advertising, campaigns in the streets, or coming to the houses. Awareness campaigns are important, as are treatment and support, as we do not know how to take care of ourselves." R

Subtheme 3: *Inadequate number of nurses*

Six out of 11 participants highlighted the positive role nurses can play in supporting the patients. They mentioned that the nurses were very kind in their dealings with the patients, and they helped them a lot. However, due to the inadequate number of nursing staff, nurses were unable to give adequate information and explanation to them. For example, one participants said:

"The nurses have a big load, and the number of nurses is very few; some of them prepare the medicine, and some of them give the *medicine, and they have to run here and there; so they are not able to catch up with the questions from patients."* W

Subtheme 4: *Need for nutritionists*

Nine out of 11 participants were not satisfied with the dietary information given to them and as a result, felt confused by the inconsistent guidance on food choices. As a result, many turned to the internet for advice. For example, one participant said:

Table II: Item rating of psychosocial needs in terms of importance and satisfaction

Needs Category/Items	Number of participants who rated item as "important" or "very important"	Number of participants who rated item as "unsatisfied" or "very unsatisfied"
Interaction with Health Professionals		
Confidence in the health professionals I meet	145*	19
Health professionals have time to discuss issues with me	145*	67
Easy and quick access to doctors	142*	60
Honest information	150*	16
Health professional who treats me with respect	152*	7
Information given sensitively	136*	27
Health professionals who listen to me	142*	62
Easy and quick access to health professionals other than doctors	77	68
Opportunities to participate in choices around treatment	103*	51
Median score	142	51
Information Needs		
Information about treatment plans	147*	44
Information about what to expect	142*	59
Information about medication and side effects	139*	61
Advise on what services help are available	136*	83
Access to other sources of information	122*	73
Median score	137	61
Support Networks		
Support from family	157*	16
Support from friends	132*	23
Support from care professionals	125*	39
Someone to talk to	151*	19
Support from neighbours	80	69
Median score	132	23
Identity Needs		
Help in maintaining independence in the face of illness	123*	33
Help in maintaining a sense of control in my life	123*	37
Support in dealing with changes in my body	134*	44
Support in dealing with any changes in the way others see me	108*	44
Support in dealing with any changes in my sense of who I am	121*	44
Median score	123	44
Emotional and Spiritual Needs		
Hope for the future	149*	17
Help with any fears	147*	35
Help in dealing with the unpredictability of the future	105*	59
Time for myself	138*	54
Helping with finding a sense of purpose and meaning	147*	25
Help with any sad feelings	136*	26
Help in dealing with the feelings of others	100*	54
Opportunities for personal prayer	147*	14
Opportunities for meeting others who are in a similar situation	137*	27
Help with any loneliness	118*	36
Support from people of my faith	129*	34
Help with any anger	99*	47
Support from a spiritual advisor	104*	51
Help with any feelings of guilt	69	61
Help in considering my sexual needs	90*	67
Median score	129	36
Practical Needs		
Help with any distressing symptom	144*	40
Help with transport	115*	95**
Help in dealing with any tiredness	139*	37
Advice about food and diet	153*	102**
Help with housework	147*	29
Help with getting out and about socially	99*	59
Help with financial matters	149*	113**
Help in filling out forms	53	60
Median score	141.5	59.5
Childcare Needs		
Help with childcare	93*	50

Note:
1.* An item is defined as "significant" if it is rated as "important" or "very important" by more than 50% (i.e., n = 84) of the 167 participants.20
2.**Similarly, an item is defined as "unmet" if it is rated as "unsatisfied" or "very unsatisfied" by more than 50% (i.e., n = 84) of the 167 participants.[20]

Table III: Maslow's hierarchy of needs of young women with breast cancer in Syria as evidenced from findings in both phases of this study

Maslow's hierarchy of needs	Findings from Quantitative Survey (Phase 1)	Findings from Semi-structured qualitative interviews (Phase 2)
Self-actualization	Needs related to "…finding a sense of purpose and meaning" was also identified as a significant need (88.0%) that remained unmet for a subset of participants (i.e., 25 participants, 15.0%)	Some participants expressed their emotional struggles that prevented them from pursuing long-term goals
Esteem needs	"Support in dealing with changes in body" was identified as a significant unmet by 44 participants (26.3%). Similarly, needs related to maintaining independence, and control in life were still identified as significant unmet needs for a subset of participants.	Participants highlighted the psychological impact of mastectomy, loss of femininity, and body image issues. One participant stated, "…the lady misses a feminine part of her body, (and) …it becomes a burden." Chemotherapy-related hair loss further added to self-esteem challenges.
Belonginess and love needs	A significant proportion of participants identified "support from family" (94%) and "someone to talk to" (90.4%) as significant needs. Emotional support and interaction with health professionals also rated highly as significant needs (e.g., "health professionals who listen to me" rated as a significant need by 136 out of 167 participants, or 81.4%).	Participants described the emotional toll of societal stigma surrounding breast cancer, which strained their relationships and social support systems. Stories of bullying and negative social interactions further illustrate the unmet social belonging needs.
Safety and health needs	"Help with financial matters" is the most unmet need (67.7% unmet), highlighting the absence of financial security. A significant proportion of participants identified challenges with access to reliable doctors (86.8%) and other healthcare professionals (85.0%) and information on their treatment plans (88.0%) as significant needs.	Participants described the inability to access consistent and affordable treatment, with some turning to desperate measures such as selling assets. Stress caused by living in a crisis environment (e.g., disruptions to electricity, overcrowded hospitals) undermines stability and health.
Physiological needs	High level of unmet practical needs such as "advice about food and diet" (61% unmet) and "help with transport" (56.8% unmet), and income distribution with 83.8% of participants earn $50 or less monthly. This suggests severe limitation in accessing nutritious food and transportation.	Expressed frustration over their inability to afford healthy foods (e.g., "avocado costs 25,000 Syrian lira per kg, which is unaffordable"). Having to resort to desperate measures such as using emergency savings.

"It is very necessary for nutritionist to be available as part of the treatment plan of cancer patients because the patients sometimes understand the information wrong." A

Subtheme 5: *Effects of unmet informational needs*
Seven out of 11 participants indicated that receiving inadequate information about the disease and the treatment side-effects had negatively affected them physically and psychologically, lessened their confidence in the doctors and the treatment, and, as a result, made them more stressed. For example, one participant said:

"He made me hate the medicines, the doctors, and the hospitals. I started to ask if any doctor I go to would be like him. What can I gain from this doctor? They can prescribe the medicine to me, and the nurses in the department will then give it to me. That's all. He made me stressed and have no confidence.". Ra

Theme 2: *Psychological challenges*
All the participants in this study expressed the importance of being psychologically comfortable because they believe that it can adversely impact the cure and recurrence of the disease.

Subtheme 1: *Uncertainty of the Future*
All participants shared feelings of uncertainty and anxiety regarding their future; the unpredictability of life and fear over the impact of potential disease recurrence. For example, one participant said:

"I am fearful of recurrence, and everyone is feeling fearful of recurrence. It is impossible to find someone who is not afraid. But I don't show that, and I don't talk about that in front of my family in order not to make them think I am scared." - L

Subtheme 2: *Fear of disease transmission to loved ones*
Three out of 11 participants were concerned about the genetic risk of their children developing cancer. For example, one participant, after discovering her disease postpartum, asked her doctor about the potential transmission to her child through breastfeeding and said:

"Look how scared I am. I was pregnant with my son, and I thought that I might have had this lump many years ago, so I asked the doctor if this could affect my son because I was pregnant at that time and I also fed him from the breast. He said, No, it would not." - Ra

Subtheme 3: *Fear of death*
Six out of 11 participants feared dying and leaving their children motherless, concerned about their children's future and care. They expressed their desire to keep on living mainly for the reason to raise their children. For example, one participant said:

"The children were the most important thing I thought about when I went for the surgery. I started thinking, if I died, what would happen to them? For example, they would be orphaned, and the people would sympathise with them. No, I would never deprive them of anything." RI

Subtheme 4: *Treatment-related effects and the loss of a woman's identity*
All participants described their difficult experiences with the treatment, specifically the mastectomy and chemotherapy. They expressed that they have experienced a lot of physical and psychological issues that have affected their lives and those of their families. The most distressing experience was the mastectomy, which altered their body image, caused a loss of sense of femininity and self-confidence, and altered their self-esteem, as stated by this participant:

"Look, the lady misses a feminine part of her body; I think she feels something is missing. She loses self-confidence, specifically if she is married. Life got more exhausting; you have to take care of the issue of the breast by putting on pads. It becomes like a burden, and you have to attend to it." - RA

Seven out of 11 participants found chemotherapy distressing with experiences of severe side effects such as hair loss, which can be especially difficult for those who valued their long hair. This affected not just the individuals but also their loved ones too. For example, one participant said:

"As my hair began to fall out, I became distressed and lashed out at those around me. I would become irritable and upset others with my words. This even led to me to avoid my fiancé when my hair loss started. I couldn't bring myself to accept my appearance, not even 1%."- W

Subtheme 5: *Inadequate psychological care*
All the participants expressed that they had not received adequate psychological care at the hospital because of the workload of their oncologists and nurses. They highlighted the need to involve psychologists and sociologists in the treatment plans of cancer patients, specifically in the distressing conditions they live in. As said by this participant: *"There should be a psychologist to support the patients psychologically and socially."* – L

Theme 3: Financial challenges

Subtheme 1: *Treatment not available and is expensive*
All participants reported difficulties accessing treatment at hospitals as well as the financial burdens in purchasing these expensive medications. Some had to resort to selling assets like gold and houses, while others used their emergency savings for treatment. For example, one participant said:

"Honestly, my family helped me partially. I also sold a gold ring, and my husband has also been putting some money aside for urgent events, so we were able to pay for the cost of this expensive medicine." - L

Subtheme 2: *Low incomes and high cost of living*
All participants mentioned that the Syrian crisis had significantly increased living costs and devalued the local currency, making it hard for low-income individuals to afford a healthy diet due to the need to prioritize their children's needs. As one participant said:

"I told you if you want to eat healthy food, you cannot, for example, eat an avocado, which is said to be very beneficial for us. When I asked about its price, it was 25 thousand Syrian lira per kg, so I cannot afford to buy it at this price." - Ri

Theme 4: Societal Influences

Subtheme 1: *Society's view and stigma*
All participants also talked about the negative social stigma associated with breast cancer, including the prevailing misconceptions that cancer is contagious or akin to getting a death sentence. These beliefs had not only negatively impacted them but also their families and children as well. For example, one participant said:

"The people around them tell them that their mother is a cancer patient, and she will not live for a long time; she will die. My older child's friends think that at any moment when he comes to the house and may not find me anymore." - A

They also expressed the distress feelings resulted from negative and annoying comments encountered during their social interactions. As stated by one participant:

"For example, they say, look, how she shaved her hair like crazy? I was hearing these words on the bus and at the bus station. The way that people bully you is very ugly; they don't know your reasons." - W

Subtheme 2: *Lack of marriage choices*
Two out of 11 participants also expressed doubt over the prospect of marriage due to the fear of societal stigma as well as the potential partners' acceptance of their physical changes. For example, one participant said:

"Who wants to marry a sick woman who has undergone a mastectomy, will be in long-term treatment, and has become deformed in her body?" H

Theme 5: Environmental Stressors

Subtheme 1: *Stressful Hospital Environment*
All participants said that the hospital environment was stressful and inadequately equipped. They also cited overcrowding as a source of stress, suggesting the necessity for a more patient-friendly setting. For example, one participant said:

"The hospital environment should be better and more organized than this. Very crowded and chaotic, and it is not tolerable". - Ra

Subtheme 2: *Situational factors*
All participants reported living under significant stress due to the breast cancer at a young age and the disrupted basic utilities like electricity, water, gas, and fuel are additional situational factors that further exaggerated the environmental stress. The disruptions in electricity supply were particularly distressing and affected their ability to cope with extreme weather after chemotherapy. As described by one participant:

"After chemotherapy, you hope for a cool environment, maybe just to use a fan, but you can't because there's no electricity or water." - A

DISCUSSION

Similar to previous studies,[19-20] practical needs were found to be a significant category of unmet psychosocial need. This is because disruption caused by breast cancer diagnosis and treatment at such a young age can adversely affect their personal development and career,[4,14,20] suggesting that meeting these practical needs can be very challenging, especially for financial needs, as demonstrated in both phases of this study. Coincidentally, it was also found that the psychosocial needs identified in this study can be mapped using the Maslow's hierarchy of needs theory. This implies that the impact of war crisis can have a cascading effect on various dimensions of the psychosocial needs of young women with breast cancer, ranging from the basic physiological needs to self-actualization needs.[21]

For example, given the high costs associated with cancer treatment, "Help with financial matters" was rated by 67.7% of the participants to be a significant unmet need in Phase 1 of study, consistent with similar past studies.[2,10,13,22-24] Additionally, the income data from the quantitative survey (Phase 1) shows that many participants were living in extremely precarious financial situation (e.g., a significant proportion of participants (83.8%) reported a monthly income of $50 or less). This financial fragility consistently aligns with the unmet financial needs expressed by many participants in the qualitative interviews as well. This is vividly illustrated through stories of participants selling personal belongings to cover treatment costs.

Furthermore, the unmet needs for transport and dietary advice in the quantitative survey are likely to be indirectly consistent with their financial struggles as well. For example, many participants (particularly those who stayed outside of Lattakia) explicitly mentioned the financial barriers they faced in their long-distance travels to seek treatment. In fact, one participant described the devaluation of the local currency and the unaffordability of nutritious food items like avocados, which further reinforce the finding that financial needs were a predominant concern. The lack of financial resources results in challenges in meeting basic physiological needs as well as their sense of security in Maslow's hierarchy of needs such as food, clean water, paying for utility bills, and fuel. The aggressive cancer treatments, alongside the challenging living conditions and financial strains in Syria, also intensify the critical strain in the psychological needs of Maslow's hierarchy of needs. A number of past studies have shown that younger women experienced significantly more psychological challenges compared to older women. [13,14,18,20,25]

Third, the unmet social needs of participants in this study also reflect their dissatisfaction with their roles as mothers or wives and affected their belongingness and intimate relationships needs in Maslow's hierarchy of needs. This issue is consistent with findings on sexual problems and social isolation[12,20] and is exacerbated by the stigmatization of cancer in Syrian society including the fear of not able to get married. In fact, such stigmatization has also been observed in the broader context of the Arabic communities.[12,26-28]

Fourth, some participants were also dissatisfied with their post-mastectomy appearance and desired for breast reconstruction. This reconstruction was essential to boost their self-esteem (as in Maslow's hierarchy of needs), as well as their prospects for marriage.[29-31] The unmet need of breast reconstruction to improve their quality of life,[32] coupled with financial constraints and other psychosocial needs, all of which, can escalate into complex psychosocial challenges with unfulfilled self-actualization needs.

This study has some pertinent limitations. First, as the participants in this study were exclusively young women with breast cancer from a single hospital in Latakia, this might have limited its generalizability to older women with breast cancer or those from different geographical locations, both within and outside of Syria. Second, the reliance on self-administered data in the quantitative phase may be susceptible to response bias, where participants might have provided more socially desirable answers. Third, there seems to be an apparent inconsistency between the Phase 1 quantitative and Phase 2 qualitative findings. In Phase 1, only three significant needs were rated as unmet, whereas Phase 2 revealed that many participants had explicitly reported more unmet needs. Whilst this discrepancy could stem from comprehension issues in responding to the questions in both phases, it could also be due to the fact that quantitative data reflects overall trends by aggregating the composite responses from all participants, but qualitative data captured the detailed, nuanced individual lived experiences. Furthermore, this discrepancy could also be due to selection bias where participants who were willing to be interviewed may have had stronger need to vent out their negative experiences, thus, potentially skewing the qualitative findings toward highlighting more unmet needs.

CONCLUSION

This study revealed a multidimensional impact of the Syrian crisis on these women's ability to meet their basic, safety, and relational needs, as perceived through the lens of Maslow's hierarchy of needs. The cascading effects of unmet financial and informational needs disrupted their emotional well-being, social belonging, and self-esteem, preventing many from achieving personal growth and self-actualization. Therefore, healthcare providers and policymakers must prioritize integrated interventions to address these psychosocial needs holistically.

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Developing a time series prediction modelling for dengue in Kota Kinabalu, Sabah

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ABSTRACT

Introduction: Dengue is a major public health issue, with 3,900,000 people living in 129 dengue-endemic countries globally facing a risk of contracting dengue fever. Dengue incidence in Sabah is among the highest in Malaysia. In 2022, Kota Kinabalu District reported 22% of the total number of dengue cases in Sabah. The objective of this study was to develop a prediction model for dengue incidence using meteorological, entomological, and environmental parameters in Kota Kinabalu, Sabah.

Materials and Methods: An ecological study was conducted from 2016 to 2021 using the dengue database and meteorological data. The forecasting model for dengue incidence was performed with R software using the seasonal autoregressive integrated moving average (SARIMA) model. The model was fitted based on the reported weekly incidence of dengue from 2016 to 2020 and validated using data collected between January and December 2021.

Results: SARIMA (1,1,1) (1,1,0)52 with the external regressor maximal temperature, Aedes index, and vacant lot were the models with minimal measurement errors, as indicated by the Mean Absolute Error (MAE) values of 3.04, Root Mean Squared Error (RMSE) of 4.43, and Akaike Information Criterion (AIC) of 1354.82.

Conclusions: The predicted values in 2021 accurately forecasted the capability to serve as an early warning system for proactive dengue measures. This information is deemed valuable to healthcare administrators for enhancing the level of preparedness.

KEYWORDS:
Dengue, environmental parameters, entomological parameters, meteorological parameters, prediction modelling

INTRODUCTION

Dengue fever is a viral infection transmitted by infected female Aedes mosquito bites from humans to humans and occurs in tropical and subtropical areas of the world. According to the World Health Organization (WHO) reports on dengue fever, 3,900,000 people live in 129 dengue-endemic countries globally and are at risk of contracting dengue fever.[1] The Western Pacific Region represents 75% of the global disease burden. The number of dengue cases in the Western Pacific Region increasingly doubled from 200,000 people in 2011 to more than 450,000 people in 2015 and 680,000 people in 2019.[2]

Kota Kinabalu had the highest occurrence of dengue cases in Sabah compared to the other districts.[3] Even though the Ministry of Health (MOH) has comprehensive guidelines for the management and treatment of dengue fever, the number of dengue cases in Kota Kinabalu has risen from 2012 to 2021. To meet the objectives of the National Dengue Strategic Plan, which aims to reduce the burden and threat of dengue through effective, locally adapted, and sustainable vector control, Kota Kinabalu district should establish its own framework to anticipate and respond accordingly.[4]

The unpredictable nature of dengue outbreaks presents challenges for public health authorities in terms of resource allocation and preparedness. Advanced predictive modelling techniques have emerged as promising methods for forecasting dengue outbreaks, allowing timely intervention and improved disease management. With prediction, early notification of the dengue epidemic and timely allocation of scarce resources for dengue management in the Kota Kinabalu District Health Office. Thus, dengue cases can be reduced and control improved, while the Kota Kinabalu Vector Borne Diseases Unit can focus more on prevention activities.

The use of autoregressive integrated moving average (ARIMA) modelling, in conjunction with time-series analysis, has become increasingly important in epidemiological research, specifically in the study of infectious diseases, such as malaria, influenza, COVID-19, tuberculosis, and dengue fever. A study in Wuhan, China presented an analysis of the epidemiology of influenza viruses in children over the influenza seasons (2007-2015) to forecast the future positive rate of various types of influenza viruses.[5] In Pakistan, ARIMA, SARIMA, and the Holt-Winter method are used to

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forecast malaria cases.6 This study aimed to identify covariates that could be used to develop a model for predicting dengue outbreaks in Kota Kinabalu to facilitate timely outbreak notification and resource management.

MATERIALS AND METHODS

Kota Kinabalu, the capital city of the state of Sabah, served as the research site because it has the highest rate of dengue fever among all districts.[3] This was an ecological study design involving eDengue data, which included vacant lots, construction sites, Aedes species, Aedes indices, dengue case data, and meteorological parameters collected from 3rd January 2016 to 25th December 2021 from the Kota Kinabalu Meteorological Office. Daily data for all years were categorized into weekly data based on epidemiological weeks.

The dengue surveillance data from the eDengue and meteorological parameters were input into Microsoft Excel. The analysis was conducted by aggregating daily data into weeks based on epidemiological weeks (with an epidemiological week beginning on Sundays).[7] The data were analysed in R programming software, utilizing the forecast, tseries, and ggplot^2 packages. Time-series data were decomposed into fundamental components and seasonal components described using an addictive method 8 as in Figure 1.

Augmented Dickey-Fuller (ADF) and Kwiatkowski–Phillips–Schmidt–Shin (KPSS) tests were applied to determine the stationarity of data.[9] Subsequently, the dataset was split into training and testing datasets. The training dataset spans from 1st March 2016 to 27th December 2020 whereas the testing dataset covers the period from 28th December 2020 to 19th December 2021. This study utilised Auto ARIMA for selecting the best ARIMA model parameters (p, d, q) by testing different combinations of parameters and comparing model performance based on information criteria like the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC).[10]

The accuracy of the model was verified by measuring the errors of the ARIMA model, such as the Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), and Akaike Information Criterion (AIC) with an external regressor. The correlogram and Ljung-Box test were employed to assess the correlation between the consecutive forecast errors.[11] A p-value below a predetermined significance level suggested the presence of autocorrelation in the values. If the p-value is greater than 0.05, it can be inferred that the residuals of the data are independent.[10] The chosen model, referred to as the predictive model, was then applied for data forecasting. This approach, however, utilizes a static learning model, which has limited applicability in public health contexts.

RESULTS

Descriptive time series of dengue cases and independent variables

Figure 2 shows the time series between meteorological parameters and dengue incidence over the study period. The weekly maximum temperature at Kota Kinabalu fluctuated between 2016 and 2021. The highest temperature was 33 °C in January 2020 and the lowest in May 2016 (35.6 °C).

This study investigated relative humidity (RH) as a climatic factor under examination. The minimum weekly humidity in Kota Kinabalu fluctuated within a relatively narrow range. The maximum RH recorded in January 2020 was 76.4%. The lowest recorded cases occurred at a RH of 77.7% in May 2016, as depicted in Figure 2.

The increase in the number of dengue cases can be attributed to weekly maximum rainfall. The weekly maximum rainfall in Kota Kinabalu between 2016 and 2021 can be classified as falling within the medium. In January 2020, the recorded maximum dengue fever case rate was 12.2 mm/hour, while the minimum case rate was observed at 10.88 mm/hour.

The distribution of the dengue vector Aedes aegypti is potentially influenced by wind speed. In January 2020, the incidence of dengue cases peaked at a rate of 4.6 knots of wind speed. The minimum recorded number of cases, as illustrated in Figure 2, was 4.9 knots during May 2016.

The time-series analysis presented in Figure 3 illustrates the relationship between the entomological parameters and dengue incidence throughout the study period. The weekly population of Aedes albopictus in Kota Kinabalu from 2016 to 2021 exhibited minimal fluctuations on a weekly basis. The peak incidence of Aedes albopictus infection occurred in January 2020, with a weekly count of 61. Conversely, the lowest recorded incidence of Aedes albopictus was observed in May 2016, with no reported instances.

This study examined the Aedes Index as a variable of interest within the field of entomology. Analysis of the weekly Aedes Index data in Kota Kinabalu revealed minimal fluctuations. In January 2020, the weekly Aedes Index reached 69. Notably, the lowest recorded weekly Aedes Index of 0 was observed in May 2016, as illustrated in Figure 3.

This study investigated vacant lots as an environmental parameter. The weekly number of vacant lots in Kota Kinabalu varied. In January 2020, 11 vacant lots were recorded weekly. Figure 3 illustrates the occurrence of the lowest recorded cases of the weekly number of vacant lots in May 2016, which amounted to 29.

Furthermore, the increase in the number of dengue cases could be attributed to the weekly number of construction sites. The weekly frequency of construction sites in Kota Kinabalu from 2016 to 2021 can be categorised as belonging to a small range. In January 2020, the highest recorded incidence rate of dengue fever was zero, whereas the lowest incidence rate of dengue cases was zero.

Developing Seasonal Autoregression Integrated Moving Average (SARIMA) model with External Regressor

An external regressor was introduced to the SARIMA models with the parameters (1,1,1) (0,1,1) and (0,1,2) (0,1,1) after selecting the two best models. The maximum temperature, Aedes index, vacant lot, and Aedes albopictus, which exhibited an association with dengue cases, were all included

Table I: Measurement errors of the SARIMA model with external regressor

SARIMA model (1,1,1) (0,1,1) with external regressor	Measurement Error		Ljung-Box Test	
	MAE	RMSE	AIC	p-value
Maximal Temperature, Aedes Index, Vacant Lot, Aedes Albopictus	3.036	4.430	1356.81	0.045
Maximal Temperature, Aedes Index, Vacant Lot	3.029	4.457	1357.40	0.047
Maximal Temperature, Vacant Lot, Aedes Albopictus	3.038	4.430	1354.82	0.045
Aedes Index, Vacant Lot, Aedes Albopictus	3.053	4.436	1355.41	0.039
Maximal Temperature, Aedes Index	3.312	4.797	1385.36	0.248
Maximal Temperature, Vacant Lot	3.341	4.925	1396.79	0.192
Maximal Temperature, Aedes Albopictus	3.316	4.776	1383.21	0.197
Aedes Index, Vacant Lot	3.036	4.466	1356.23	0.040
Aedes Index, Aedes Albopictus	3.387	4.875	1385.11	0.156
Vacant Lot, Aedes Albopictus	3.054	4.436	1353.41	0.039
Maximal Temperature	3.630	5.283	1423.98	0.373
Aedes Index	3.398	4.920	1385.66	0.198
Vacant Lot	3.342	4.947	1396.64	0.162
Aedes Albopictus	3.393	4.881	1383.12	0.153
External Regressor	**Measurement Error**		**Ljung-Box Test**	
SARIMA model (0,1,2) (0,1,1) with external regressor	**MAE**	**RMSE**	**AIC**	**p-value**
Maximal Temperature, Aedes Index, Vacant Lot, Aedes Albopictus	3.051	4.451	1358.79	0.087
Maximal Temperature, Aedes Index, Vacant Lot	3.038	4.458	1357.40	0.077
Maximal Temperature, Vacant Lot, Aedes Albopictus	3.047	4.451	1356.81	0.086
Aedes Index, Vacant Lot, Aedes Albopictus	3.060	4.454	1357.04	0.084
Maximal Temperature, Aedes Index	3.336	4.869	1387.66	0.224
Maximal Temperature, Vacant Lot	3.349	4.944	1398.47	0.193
Maximal Temperature, Aedes Albopictus	3.309	4.794	1384.88	0.183
Aedes Index, Vacant Lot	3.043	4.490	1358.43	0.076
Aedes Index, Aedes Albopictus	3.462	5.001	1386.33	0.157
Vacant Lot, Aedes Albopictus	3.056	4.454	1355.07	0.084
Maximal Temperature	3.618	5.300	1424.93	0.346
Aedes Index	3.498	5.081	1387.33	0.197
Vacant Lot	3.340	4.961	1397.84	0.187
Aedes Albopictus	3.463	5.002	1384.33	0.157

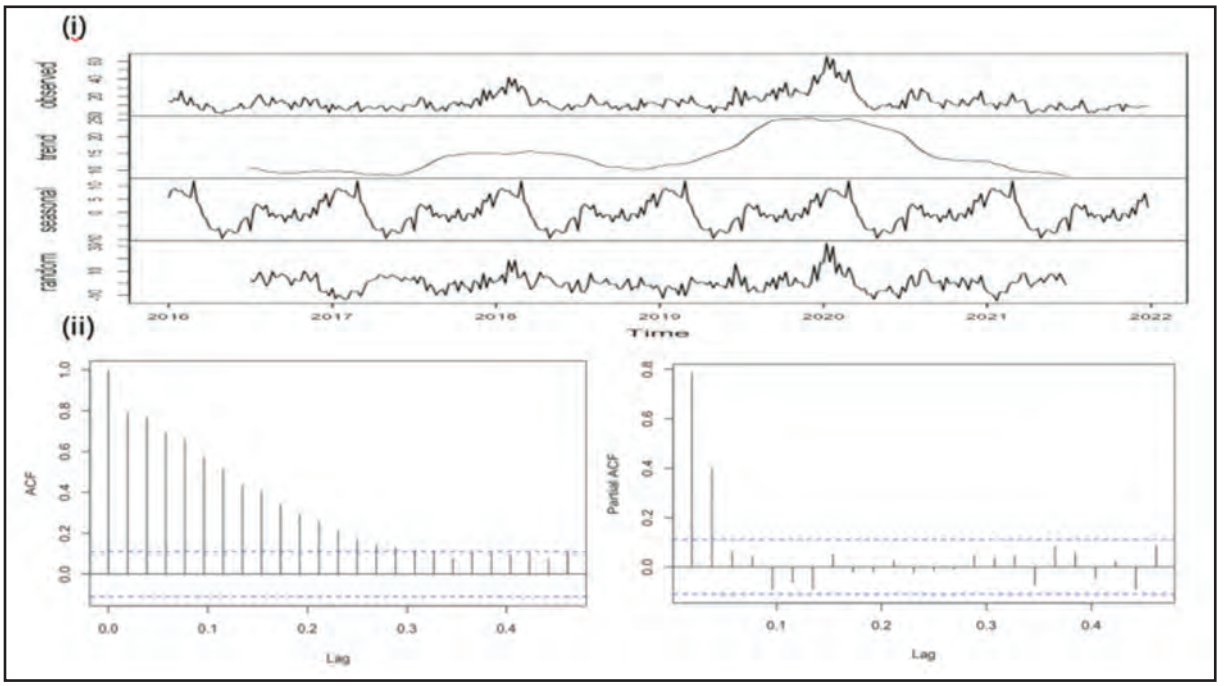

Fig. 1: (i)Decomposition of dengue cases reported years 2016 – 2021 (a) Time series of dengue cases in Kota Kinabalu 2016-2021 (b) Trend of dengue cases in Kota Kinabalu 2016-2021 (c) Seasonality of dengue cases in Kota Kinabalu 2016-2021 (d) Random of dengue cases in Kota Kinabalu 2016-2021
(ii) ACF plot of and PACF plot for time series of dengue cases in Kota Kinabalu from 2016 to 2021

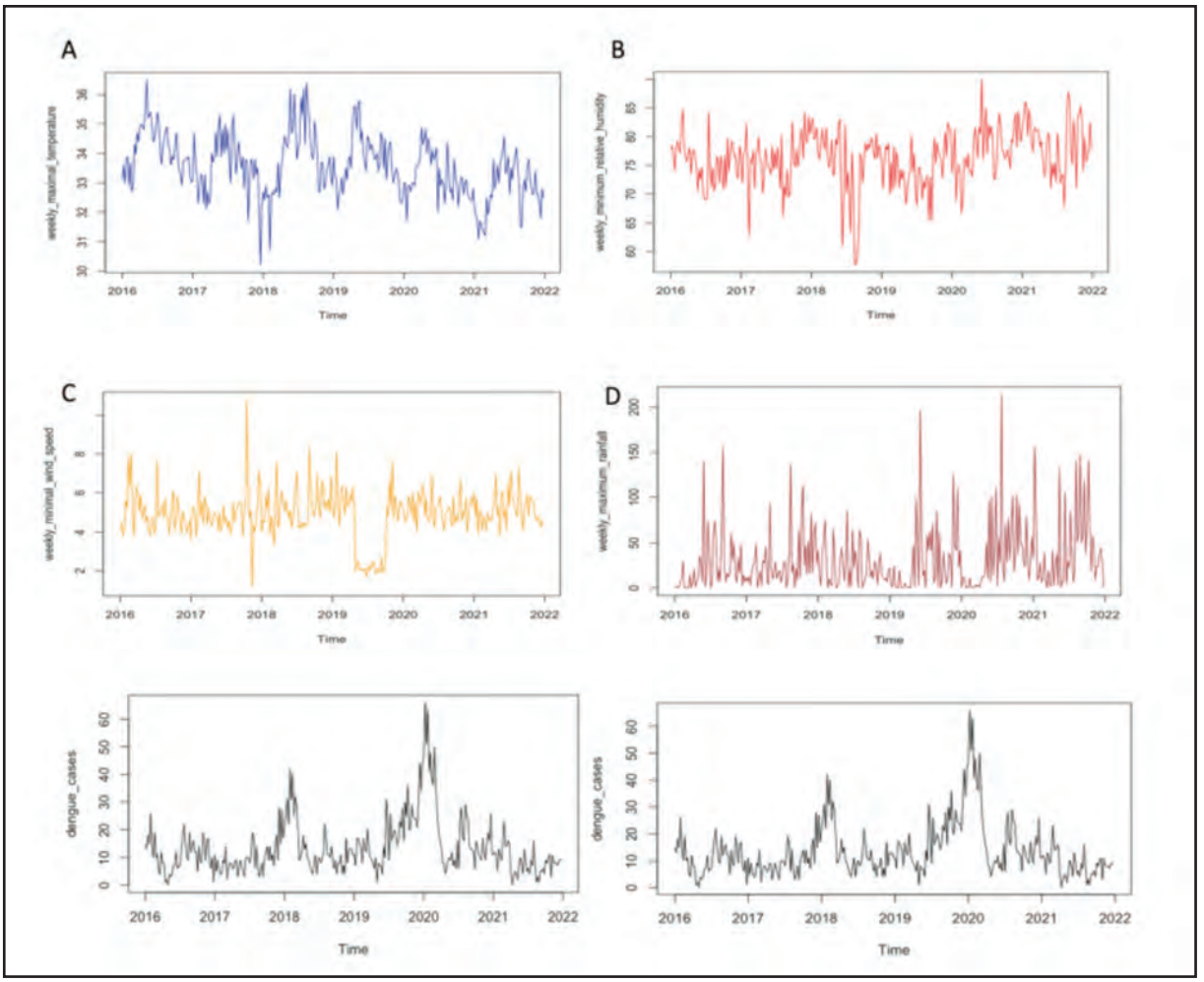

Fig. 2: Time Series of Dengue Cases in Kota Kinabalu Sabah years 2016 to 2021 and meteorological variables A) weekly maximum temperature (blue line); B) weekly minimum relative humidity (red line); C) weekly minimum wind speed (yellow line) and D) weekly maximum rainfall (brown line)

in the external regressor. SARIMA models (1,1,1) (0,1,1) and (1,1,2) (0,1,1) were constructed using the external regressors Aedes albopictus, Aedes index, vacant lot, and maximal temperature.

Among the 28 SARIMA models with external regressors, as shown in Table I, was determined to be SARIMA (1,1,1) (0,1,1) with the external regressors of maximum temperature, vacant lot, and Aedes Albopictus identified as the best model. This decision was based on the minimal measurement error, as indicated by the Mean Absolute Error (MAE) of 3.04, Root Mean Squared Error (RMSE) of 4.43, and Akaike Information Criterion (AIC) of 1354.82.

Although the MAE value of the model with external regressors (maximum temperature, vacant lot, and Aedes Index) was slightly higher than that of the SARIMA models (1,1,1) (0,1,1), the RMSE and AIC values were the lowest among all models. The p-value of the Ljung-Box test exceeded 0.05, indicating a lack of significant evidence to reject the null hypothesis. The residuals of the model exhibited an independent distribution, and no significant serial correlation was observed in the data. Additionally, the inclusion of these three external regressors has the potential to enhance the model.

The residual correlogram exhibited oscillations within the range of +10 to -10 during the early and middle months of 2018 and the initial months of 2021. Additionally, slight deviations surpassed these thresholds in both the positive and negative directions. The plot of the autocorrelation function (ACF) displays the residual data within the specified boundaries, with notable peaks observed at lags of 9, 38, 39, and 55. The residual value demonstrated a normal distribution, with a mean residual value of zero.

The figure presented in Fig.4 depicts the visualisation of the forecast for SARIMA models (1,1,1) (0,1,1) incorporating external regressors, such as maximum temperature, vacant lot, and Aedes Albopictus, along with the residual of the model. The observed line (red line) exhibited a consistent pattern of fluctuation, which was also observed in the prediction line (blue line) despite the latter being positioned at a higher level. The model demonstrated reliable

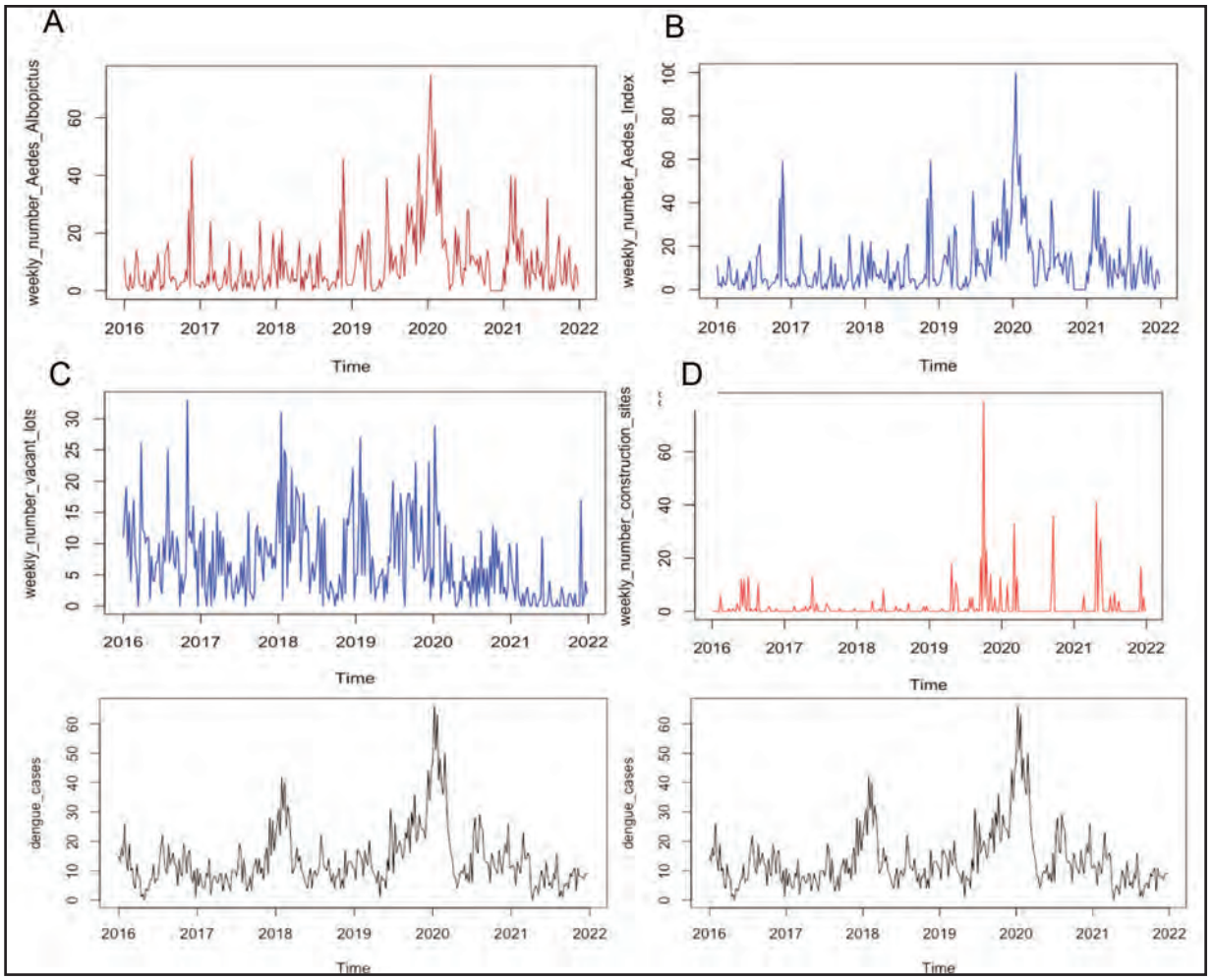

Fig. 3: Time Series of Dengue Cases in Kota Kinabalu Sabah years 2016 to 2021 and entomological variables A) weekly number of Aedes Albopictus (brown line); B) weekly number of Aedes Index (blue line); C) weekly number of vacant lot (blue line); D) weekly number of construction (red line)

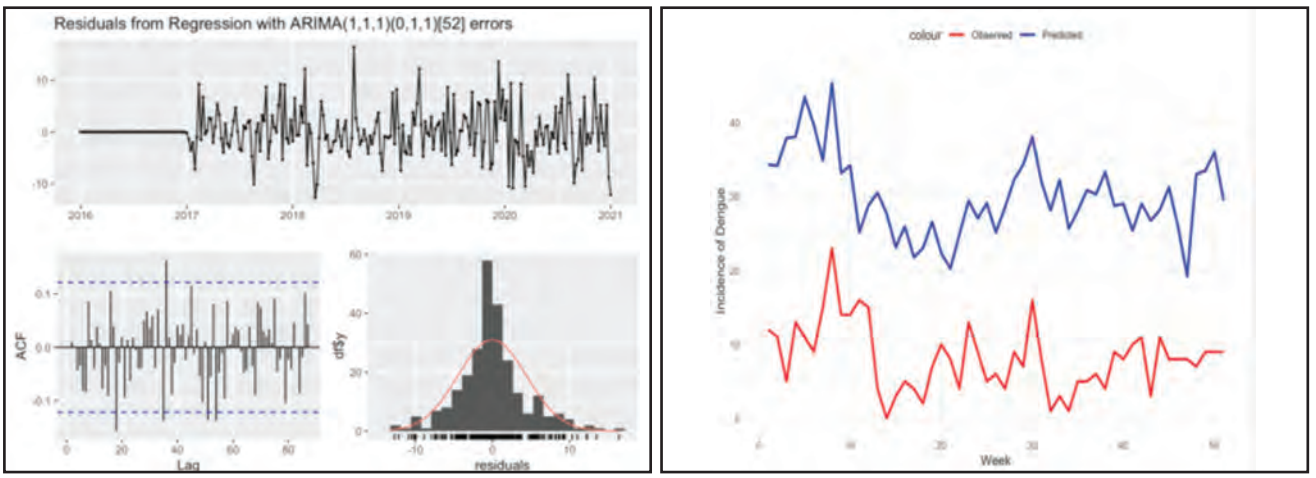

Fig. 4: Forecasting of the SARIMA model (1,1,1) (0,1,1) with external regressors of maximum temperature, vacant lot, and Aedes Albopictus and residual of the model

forecasting abilities, though it tended to slightly overestimate cases, likely due to the impact of COVID-19 on data patterns in 2021. Despite this, it showed potential as an early warning system for predicting dengue cases in Kota Kinabalu. Therefore, the SARIMA models (1,1,1) (0,1,1), which include external regressors such as maximum temperature, vacant lot, and Aedes albopictus, were found to be the most effective in predicting dengue incidence in Kota Kinabalu.

DISCUSSION

The optimal mean temperature range favourable for mosquito development is between 25°C and 27°C.[12] Despite this study, the mean temperature was 24–35 °C and exhibited an inverse correlation with dengue incidence. Higher temperatures in warm areas could potentially have detrimental impacts on the transmission range of viruses owing to reduced vector survival, reproduction, and immature habitats.[13]

Despite the mean minimal RH of 76% in this study, an interaction exists between humidity, temperature, and availability of water sources that facilitate the creation of suitable breeding conditions.[14] The influence of wind speed on dengue transmission in confined areas may not be substantial, as mosquitoes can locate appropriate breeding grounds and human hosts, even in the presence of moderate wind speeds 15 particularly in urban areas, such as Kota Kinabalu.

An elevated Aedes index typically correlates with a heightened probability of dengue occurrence. The same was observed in Sri Lanka and Vietnam.[16,17] The Aedes Index has a significant and strong relationship with dengue cases. The species Aedes Aegypti was the most captured because it exhibited endophilic behaviour, while Aedes Albopictus was predominantly exophilic and found in outdoor vegetation.[18] As a result, the health inspector found it easier to collect larvae outside the premises than indoors, where permission was required to conduct an inspection within the house.

Many construction sites have implemented mosquito prevention methods, and construction workers and site managers have often destroyed or controlled mosquito breeding grounds. Consistent monitoring, proper drainage, sealing or eliminating sources of standing water, and application of larvicidal treatments. These steps reduce the risk of dengue and reduce mosquito density.[19] The optimal microenvironments for A. aegypti growth can be identified by minimising exposure to sunlight, increasing and closer proximity to vegetation, and shaded and vegetated surroundings, which are frequently found in vacant lots.[20]

The SARIMA model (1,1,1) (0,1,1) with an external regressor was developed using the weekly maximal temperature, vacant lot, and A. albopictus, which provided the best-suited model in this study. These findings contradict those of previous studies conducted in various countries, where temperature and humidity have been consistently identified as strong predictors of the magnitude of dengue incidence.[21] These findings were dissimilar to the findings in Bangkok. The multivariate Poisson regression model for time series data indicates that a 1% increase in rainfall is associated with a corresponding increase of 3.3% in the incidence of dengue cases in Bangkok.[22] However, in this study, rainfall was not a significant predictor. This finding was like that of a study in Makassar, which stated humidity as a strong predictor.[23]

The accuracy of SARIMA models for forecasting in 2007 improved with the inclusion of climatic variables as external regressors. Temperature significantly influenced the model's ability to forecast dengue incidence.[24,25] However, humidity did not have a notable impact in the West Indies region.[24,26]

The differences in time-series forecasting findings between different studies can be attributed to several factors, including the choice of forecasting methods from simple statistical models such as ARIMA to more advanced approaches such as exponential smoothing methods, machine learning algorithms, and deep learning models such as Long Short-Term Memory (LSTM) networks.[27] The selection of the forecasting method can significantly affect the accuracy and performance of the predictions.

Time series data can exhibit diverse characteristics such as trends, seasonality, irregular fluctuations, or long-term dependencies. The presence or absence of these patterns can influence the choice and effectiveness of the forecasting models. For example, some models may perform well for data with clear patterns, whereas others may excel at capturing complex dependencies or handling irregular fluctuations. In addition, the size and quality of the datasets used for the analysis can affect the performance of the forecasting models.[28]

During this study, the COVID-19 pandemic introduced numerous challenges, including movement control orders (MCO) imposed throughout 2020. These disruptions likely affected individuals' access to hospitals and clinics, impacting the quality of collected samples, particularly for dengue notifications within the eDengue system. Furthermore, surveillance data may have been underestimated, affecting the accuracy of model predictions. The model's training on pre-COVID data may have contributed to deviations in forecast accuracy due to changes in data patterns during the pandemic. Future analyses should include an evaluation of model performance with post-COVID data as an additional sensitivity test to improve reliability.

CONCLUSION

The incidence of dengue is expected to increase in Kota Kinabalu. Hence, it is necessary for governmental authorities, non-governmental organisations, and policymakers to implement nationwide initiatives in conjunction with current policies to address the impending challenges arising from the prevalence of dengue. Therefore, community education campaigns should be conducted to enhance public awareness. These forecasting results provide valuable insights into the number of individuals who may contract dengue in the future. This information can be used to aid public health policymakers in predicting dengue outbreaks and implementing preventive measures. Additionally, these data can inform the development of appropriate policies and

strategies to effectively manage and control future dengue outbreaks in Kota Kinabalu. The findings showed that temperature, entomological parameters, and number of vacant lots were correlated with the incidence of dengue in Kota Kinabalu. In this study, two Seasonal ARIMA models (1,1,1) (0,1,1)52 with external regressors with maximal temperature, vacant lots, and Aedes albopictus were the best-suited model to predict the future incidence of dengue fever cases in the forthcoming year, which is useful for health care administrators for better preparedness.

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ETHICAL STATEMENT

The study was approved by the Ethics Committee of University Malaysia Sabah also with approval code JKEtika 1/23 (30) and National Malaysian Research Registry (NMRR ID -23-00058- LZV(IIR)

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Diagnostic utility of pleuroscopic guided pleural biopsy versus pleural fluid cell block in the diagnosis of malignant pleural effusion

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ABSTRACT

Introduction: Pleural biopsy using flex-rigid pleuroscopy or pleural effusion cell block analysis is useful for diagnosing malignant pleural effusion. However, the current literature lacks documented comparisons between pleural biopsies and cytological cell blocks. This study aims to compare the diagnostic accuracy of pleural biopsy and cytological cell block in identifying malignant pleural effusion.

Materials and Methods: A retrospective review was conducted on patient data from those who underwent pleuroscopy at Hospital Canselor Tuanku Muhriz from January 2021 to December 2023. We included patients with pleural effusion who underwent both cell block and pleural biopsy with a confirmed diagnosis of malignancy through histopathological examination. At least 200 ml of pleural fluid was collected, followed by the biopsy of six or more pleural tissue samples.

Results: Out of the 196 pleuroscopy procedures analysed, 91 patients were diagnosed with malignant pleural effusion. Malignancy was diagnosed in 50 (54.9%) cases using cell block analysis, whereas pleural biopsy identified malignancy in 81 (89%) cases. The diagnostic yield was significantly higher for pleural biopsy compared to pleural fluid cell block [89% (81/91) vs. 54.9% (50/91); p < 0.001]. Among patients with negative results on pleural fluid cell block, 33 (36.3%) had positive results on pleural biopsy. The definitive diagnoses of malignancy included 64 (70.3%) cases of lung adenocarcinoma, 4 (4.4%) cases of lung squamous carcinoma, 2 (2.2%) cases of small cell lung cancer, 2 (2.2%) cases of mesothelioma, and 19 (20.9%) cases of metastatic carcinoma. Eight (8.8%) patients exhibited negative findings on both pleural fluid cell block and pleural biopsy. Further diagnoses were achieved through computed tomography-guided needle tru-cut biopsy of the lung in 6 patients (6.6%), transbronchial lung biopsy in 1 patient (1.1%), and cervical lymph node biopsy in 1 patient (1.1%).

Conclusion: Pleural biopsy exhibits superior diagnostic accuracy compared to pleural fluid cell block analysis for malignant pleural effusion. In cases where cell block results are negative but suspicion remains high, pleural biopsy remains a crucial diagnostic tool.

KEYWORDS:
Malignant pleural effusion; pleuroscopy; cell block; pleural biopsy

INTRODUCTION

Determining the underlying aetiology of pleural effusion is crucial for guiding appropriate management and predicting the clinical course of malignant diseases.[1-2] Accurate diagnosis is essential for making informed decisions regarding treatment options. Thoracentesis, followed by cytosmear or cell block analysis, is commonly employed as the initial diagnostic step due to its safety and minimally invasive nature.[3] Pleural fluid (PF) cell block analysis has also emerged as a valuable alternative to pleural tissue biopsy, particularly for patients who are unsuitable candidates for flex-rigid pleuroscopic biopsy due to anatomical challenges, comorbidities, or other factors.

However, the current diagnostic pathways for pleural effusion, including cytosmear and cell block analysis, face several limitations. The reduced sensitivity of these methods can be attributed to factors such as limited morphological features, overcrowding of cells, cell loss, and variations in laboratory processing techniques.[4] These issues may contribute to false-negative results, potentially leading to delayed or incorrect diagnoses. The implications of false negatives are particularly concerning, as they can impact staging and delay timely therapeutic interventions, which may ultimately affect patient prognosis.

Although both pleuroscopic pleural biopsy and PF cell block analysis are widely used in the diagnosis of malignant pleural effusion, limited studies have directly compared their

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diagnostic efficacy. This gap in the literature highlights the need for a more comprehensive evaluation of these diagnostic modalities. This study aims to fill this gap by assessing the effectiveness of these two modalities in diagnosing malignant pleural diseases and improving clinical outcomes.

MATERIALS AND METHODS

Patients

This single-centre retrospective cohort study was conducted at Hospital Canselor Tuanku Muhriz, University Kebangsaan Malaysia, from January 2021 to December 2023. The UKM Research Ethics Committee approved the study with the ethics code JEP-2024-411. The hospital database was utilised to identify patients who underwent both cell block analysis and pleural biopsy for pleural effusion via pleuroscopy. We included only those with a confirmed malignancy diagnosis through histopathological examination. Patients with inadequate samples for either cell block or pleural biopsy, as well as those with non-malignant pleural effusion, were excluded from the study. Patient demographics, clinical profiles, chest radiography results, pleuroscopic observations, pleural fluid results and histopathological findings were recorded for analysis.

Procedure

Vital signs were recorded before the procedure. A pulmonologist, assisted by two endoscopy staff, performed flex-rigid pleuroscopy in a fully equipped endoscopy room. Conscious sedation was achieved with intravenous fentanyl and midazolam, with doses adjusted as needed.

The patient was placed in the lateral decubitus position, and the entry site was identified using the liner-type ultrasonographic probe. Topical anaesthesia with 2% lidocaine was infiltrated to the skin, subcutaneous tissue, intercostal muscle, periosteum of ribs, parietal pleura and intrapleura. The needle was carefully manoeuvred along the superior aspect of the rib, drawing a small amount of fluid first and then gradually injecting lidocaine as it advanced towards the pleura. This procedure continued until the pleural fluid was successfully drained.

The single port entry method was employed for pleuroscopy. Initially, a scalpel was utilised to create a skin incision, followed by careful blunt dissection of the intercostal muscles until reaching the parietal pleura. Subsequently, an 8 mm inner diameter rigid trocar was inserted. The inner part of the trocar was then retracted, allowing the flex-rigid pleuroscope (LTF-260; Olympus, Tokyo, Japan) to be introduced through the trocar.

The procedure comprised the following sequential steps: (1) Aspirating the pleural fluid (at least 200 ml); (2) Conducting adhesiolysis to enable thorough examination of the pleural space; (3) Examining the pleural space; and (4) Collecting multiple biopsy samples (typically 4-6) directly from any abnormal regions in the parietal pleura or diaphragm using biopsy forceps under direct visualisation.

Once satisfactory biopsy specimens were acquired, the pleuroscope was withdrawn, and a 24 Fr chest drain was inserted through the trocar and then connected to an underwater seal device.

Following the procedure, a post-procedure chest X-ray was performed. The chest tube was promptly removed upon lung re-expansion, with a minimal amount or resolution of pleural effusion confirmed by chest ultrasonography.

Biopsy specimen and cell block

Histological specimens obtained through pleuroscopy were evaluated using the standard protocol employed in the Department of Histopathology and Cytopathology. Biopsy samples were promptly fixed in formalin, processed into paraffin blocks, and sectioned. Paraffin-embedded sections underwent staining with Haematoxylin and Eosin (HE) and were subjected to immunohistochemical staining.

The pleural fluid was used to prepare conventional smears and cell blocks. For cell blocks, the fluid specimen was centrifuged at 2500 rpm for 15 minutes. The supernatant was discarded, leaving a cell pellet. Plasma, thromboplastin, and calcium chloride were added to promote clot formation. The cell pellet and clot were then fixed in 10% buffered formalin for 24 hours. After fixation, the sample was wrapped in filter paper and processed in a tissue processor. Following embedding in paraffin, the cell block was prepared, sectioned, and stained with HE. Special stains, such as PAS, were applied as needed.

Statistical analysis

Descriptive statistics were used to summarise the data, with results presented as means with standard deviations, frequencies, and percentages. To evaluate the significance of the findings, a p-value of less than 0.05 was considered indicative of statistical significance. The analysis was performed to compare and interpret the diagnostic accuracy and yield between the pleuroscopic guided pleural biopsy versus the pleural fluid cell block, ensuring that the results were appropriately summarised and evaluated based on these descriptive measures.

RESULTS

Demographic

Table I shows the demographic characteristics of the study subjects. Among the 91 patients, 46 (50.5%) were men, and 45 (49.5%) were women, with a mean age of 66.5 years (range 23-88 years).

Pleuroscopy morphology and chest drainage procedures

The mean (SD) time from referral to the pleuroscopy procedure was 3.5 (2.7) days. The median procedure duration was 30 minutes, with a range of 20 to 50 minutes. Pleuroscopic examination revealed adhesions and loculations in 8 patients (8.8%). Within our study population, pleuroscopy predominantly identified nodules on the parietal pleura. Specifically, 58 patients (63.7%) had nodules, 13 patients (14.3%) had nodules with hyperaemia, 13 patients (14.3%) had hyperemia alone, and 7 patients (7.7%) had a yellowish-white membrane.

Table I: Demographics and clinical characteristics of patients with malignant pleural disease

Variable	n = 91
Gender, no. (%)	
Male	46 (50.5)
Female	45 (49.5)
Age	
Mean (years), mean (SD)	66.5 (12.4)
Range (years)	23-88
> 60 years old, no. (%)	67 (73.6)
< 60 years old, no. (%)	24 (26.4)
Smoking history, no. (%)	
Current or former	20 (22)
Never	71 (78)
Length of stay, mean (SD)	14.6 (6.5)
Pleurodesis, no. (%)	21 (23.1)
Number of pleuroscopic biopsies, mean (SD)	8.9 (3.1)
Median chest tube drainage period (days), mean (SD)	9.9 (5.5)
Time lag from admission till pleuroscopy date	3.5 (2.7)
Tumour types, no. (%)	
Lung adenocarcinoma	64 (70.3)
Lung squamous carcinoma	4 (4.4)
Small cell lung cancer	2 (2.2)
Breast carcinoma	8 (8.8)
Ovarian cancer	3 (3.3)
Malignant pleural mesothelioma	2 (2.2)
Renal cell cancer	2 (2.2)
Lymphoma	2 (2.2)
Melanoma	1 (1.1)
Urothelial cancer	1 (1.1)
Esophageal cancer	1 (1.1)
Nasopharyngeal carcinoma	1 (1.1)
Procedure-related complications, no. (%)	
Persistent air leak	1 (1.1)
Subcutaneous emphysema	2 (2.2)
Empyema thoracic	1 (1.1)
Non-expandable lung	2 (2.2)
Re-expansion pulmonary edema	1 (1.1)
Chest tube dislodge	1 (1.1)

Table II: Radiographic and pleuroscopic characteristics of malignant pleural diseases

Variables	n = 91
The severity of pleural effusion is based on a chest radiograph; no. (%)	
Mild pleural effusion	13 (14.3)
Moderate	37 (40.7)
Massive	41 (45)
Pleural effusion laterality, no. (%)	
Right	49 (53.8)
Left	42 (46.2)
Colour of pleural fluid, no. (%)	
Straw-coloured	50 (54.9)
Haemorrhagic	41 (45.1)
Pleuroscopic findings, no. (%)	
Nodules	58 (63.7)
Nodules and hyperaemic	13 (14.3)
Hyperaemia	13 (14.3)
Yellowish white membrane	7 (7.7)
Loculation on pleuroscopic examination, no. (%)	8 (8.8)

Table III: Diagnosis of the pleural fluid by cell block and pleural biopsy

Diagnosis	Cell smear		Cell block		Pleural biopsy	
	n	%	n	%	n	%
Suspicious of malignancy	18	19.7	0	0	0	0
Malignancy	44	48.4	50	54.9	81	89
Non-specific inflammation	29	31.9	41	45.1	10	11

Chest tube drainage lasted for a mean (SD) of 9.9 (5.5) days. In patients undergoing pleurodesis, the median duration of drainage was 8 days (range, 2-23 days), whereas in those not undergoing pleurodesis, it was 9 days (range, 1–28 days). Pleurodesis was performed in 21 patients (23.1%) prior to chest tube removal.

Cytology examination and histopathological diagnosis

The definitive diagnoses of malignancy comprised 64 cases (70.3%) of lung adenocarcinoma, 4 cases (4.4%) of lung squamous carcinoma, 2 cases (2.2%) of small cell lung cancer, 2 cases (2.2%) of mesothelioma, and 19 cases (20.9%) of metastatic carcinoma. Cell block analysis identified malignancy in 50 cases (54.9%), while pleural biopsy detected malignancy in 81 cases (89%). This represents a significantly higher diagnostic yield for pleural biopsy compared to pleural fluid cell block [89% (81/91) vs. 54.9% (50/91); $p < 0.001$].

Among patients with negative results on the pleural fluid cell block, 33 (36.3%) had positive findings on pleural biopsy. Eight (8.8%) patients had negative results on both pleural fluid cell block and pleural biopsy. Diagnoses were also made in 6 patients (6.6%) through computed tomography-guided needle tru-cut biopsy of the lung and in 1 patient each (1.1%) via transbronchial lung biopsy and cervical lymph node biopsy. The radiographic and pleuroscopic characteristics of malignant pleural diseases and diagnosis of the pleural fluid by cell block and pleural biopsy are shown in Tables II and III.

DISCUSSION

Most cases of malignant pleural effusion result from metastatic spread to the pleura. Accurate differentiation between malignant pleural effusion and paramalignant effusion is essential, as it affects disease staging and treatment strategy. Flex-rigid pleuroscopy under local anaesthesia is utilised to obtain pleural tissue in cases of suspected malignant pleural disease.[5-9] Studies have reported a sensitivity of 91% and a specificity of 100% for flex-rigid pleuroscopic biopsy in diagnosing exudative pleural effusion.[5] While tissue biopsy followed by histological examination remains the gold standard, it may not always be feasible, especially for patients who are unfit for flex-rigid pleuroscopy. An alternative approach is the collection of pleural effusion cell blocks, which provides a more accessible method for diagnosis.

In this study, pleural effusions were evaluated by comparing the cell block technique with pleural biopsy methods. The primary objective was to assess the effectiveness of cell block analysis relative to pleural biopsy, which is widely recognised as the gold standard for pathological diagnosis. The British Thoracic Societypleural disease guidelines emphasise that the diagnostic accuracy for malignant pleural effusion improves when both cell blocks and smears are prepared from pleural fluid samples.[10] The American College of Chest Physicians and the National Comprehensive Cancer Network recommend pleural biopsy as the next step after at least two negative thoracenteses.[11-12]

The 2000 American Thoracic Society statement on managing malignant pleural effusions recommends pleuroscopy for exudative effusions of unknown aetiology.[13] Pleuroscopy is regarded as a safe and minimally invasive procedure, with procedure-related mortality being rare when performed by skilled practitioners.[14] However, there is a risk of life-threatening severe bleeding if intercostal vessels are injured. In our study, no mortalities or major complications were reported. A few patients experienced minor complications, including prolonged air leaks, subcutaneous emphysema, wound infections, and empyema. These findings align with previously reported complications, which commonly include persistent air leaks, subcutaneous emphysema, and infections.[15-16]

Pleuroscopy facilitates the collection of sufficient tissue specimens for histological examination and allows for the evaluation of chest wall invasion or mediastinal involvement. However, studies suggest that approximately 10% of effusions may remain undiagnosed despite pleuroscopy.[17,18] Our study's pleuroscopic diagnostic yield was lower than that reported in previous studies, which may be due to factors such as inadequate or non-representative biopsies or adhesions obstructing access to neoplastic tissues.[19] Nonetheless, our findings are consistent with Miyoshi et al., who reported that pleural biopsy using flex-rigid pleuroscopy achieved significantly higher diagnostic rates (94.2%) compared to pleural fluid cell block (71.4%) for malignant pleural disease.[20]

The cell block technique is increasingly recognised for its efficacy in effusion cytology and fine-needle aspiration cytology.[4,21] Utilizing cell blocks from pleural fluid samples offers advantages over conventional cytology by preserving morphological architecture more effectively. This method provides enhanced detail of cellular morphology, including better preservation of nuclear and cytoplasmic features, intact cell membranes, and well-defined chromatin.[22-24] Additionally, cell blocks reduce cellular dispersal, which aids in the recognition of histological disease patterns and enhances the effectiveness of immunohistochemical staining and molecular testing.[22-24] Studies have reported a wide range of diagnostic yields for cell block in detecting malignant pleural effusion, from 15% to 89.4%, with variations likely influenced by factors such as specimen size, specimen type, and aspiration techniques.[21-30] In our study, pleural fluid cell block was able to diagnose approximately 54.9% of cases. The lower yield of malignant cells in cell blocks in our study may be attributed to factors such as low cellularity and bleeding during the preparation process.

For inconclusive pleural biopsy results, advanced imaging modalities such as contrast-enhanced computed tomography (CT), positron emission tomography (PET), or PET-CT can help identify suspicious areas that may have been missed during initial sampling. These imaging techniques enhance lesion localisation and guide repeat biopsies, improving diagnostic accuracy. In addition, alternative biopsy approaches, including image-guided percutaneous needle biopsy or CT-guided biopsy of pleural or extrapleural lesions, can be employed. These methods are particularly useful for targeting areas that are inaccessible during pleuroscopy, thereby increasing the overall diagnostic yield.

Patients with suspected malignant pleural effusion should undergo stratification based on clinical suspicion, imaging findings, and individual risk factors to guide the diagnostic approach. For patients with low to moderate suspicion, pleural fluid cytology and cell block analysis should considered as the initial diagnostic modalities due to their minimally invasive nature and reasonable diagnostic yield. In cases where cell block analysis produces negative or inconclusive results, particularly in patients with moderate to high pre-test probability, pleuroscopic-guided biopsy is advised to confirm the diagnosis and ensure accuracy.

While pleuroscopy is a valuable diagnostic tool, it carries inherent risks, including bleeding and other procedural complications. To mitigate these risks, a thorough pre-procedural evaluation is essential. This includes assessment for coagulopathies, review of antiplatelet or anticoagulant therapies, and evaluation of vascular abnormalities identified through imaging. Optimising patient conditions, such as correcting coagulopathy or adjusting medications, can further reduce the likelihood of complications. Close monitoring following pleuroscopy allows for the early detection and prompt management of potential complications, such as bleeding, infection, or pneumothorax. By integrating risk stratification, appropriate pre-procedural optimisation, and vigilant post-procedural care, the safety and efficacy of pleuroscopy in diagnosing malignant pleural effusion can be maximised.

CONCLUSION

Pleural biopsy demonstrates superior diagnostic accuracy compared to pleural fluid cell block analysis in the evaluation of malignant pleural effusion. If cell block results are negative but there is still a high clinical suspicion of malignancy, pleuroscopy-guided pleural biopsy is an essential diagnostic tool. To improve clinical outcomes, we propose a diagnostic pathway where pleural fluid cytology is used as an initial screening tool to determine the need for subsequent pleural biopsy.

Future research should focus on conducting multicenter prospective studies to validate these findings across diverse populations and healthcare settings. Additionally, comparative analyses exploring the cost-effectiveness of pleuroscopy versus cell block techniques are essential to inform resource allocation and optimise diagnostic approaches.

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ORIGINAL ARTICLE

Free omental patch as the promising future for incisional hernia surgery: an experimental study in rat model

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ABSTRACT

Introduction: Incisional hernia is the common complication of abdominal surgery with serious morbidity. The use of Composite mesh (CM) is the current gold standard, which is superior to Polypropylene mesh (PPM) for closing the defect, due to its minimal intraabdominal adhesion.

In this study, we were using the novel combination of free omental patch (FOP) and PPM compared to CM for defect closure surgery in incisional hernia using rat models. We compared the gene expression of VEGF, COL3A1, COL1A1, COL1A2, and ratio of COL1A1/COL3A1 as the representative of wound healing process from all treatment options.

Materials and Methods: Eighteen wistar rats were made into incisional hernia models and divided into three groups of FOP, FOP-PPM, and CM at the 14th day. After each group underwent hernia repair, abdominal wall samples were taken to examine the expression of qPCR VEGF, COL3A1, COL1A1, and COL1A2 at the 21st day.

Results: There were no significant different in the gene expression of VEGF, COL3A1, COL1A1, COL1A2 and COL1A1/COL3A1 ratio between FOP, FOP-PPM and CM group (p-value >0.05). In addition, non-significant result also found at the comparative analysis between FOP-PPM and MC groups.

Conclusions: FOP can give the similar result as CM for defect closure surgery in incisional hernia, either when combined with PPM or as a single option. However, further clinical study is needed to support this animal study.

KEYWORDS:
Incisional hernia, collagen type 1 alpha-subunit, surgical mesh, Polypropylene mesh, composite mesh, free omental patch, ascular Endothelial Growth Factor A, Wistar rat

INTRODUCTION

Incisional hernia is a common complication of abdominal surgery with multifactorial aetiology.[1,2] It can cause significant morbidity, impair quality of life, and are costly to treat.[2] Currently, the intra-abdominal technique with Composite mesh (CM) is considered the gold standard for its defect closure, as it effectively withstands intra-abdominal pressure and has a low risk of gastrointestinal adhesions.[3] It has its "biface implants" with a porous external surface to encourage tissue integration and a smooth microporous internal surface to prevent adhesions when placed in contact with viscera. Pedicled omental patch is widely used to close several defects on the abdomen, as it can promote wound healing. However, pedicled omental patch is limited in range. The using of free omental patch had been studied for the defect closure of farther distance of intraabdominal defect, such as perforated gastric or duodenal ulcer.[4] However, the usage of free omental patch to close the defect of incisional hernia need to be studied.

This study aims to compare the efficacy of free omental patch, combination of polypropylene mesh with free omental patch, and composite mesh in the closure of incisional hernia defects. We evaluated wound healing by assessing the expression of Vascular Endothelial Growth Factor (VEGF), COL3A1, COL1A1, COL1A2, and COL1A1/COL3A1 ratio which are involved in proliferative and remodelling stage of wound healing by inducing angiogenesis, tissue fibrosis, and collagen formation.[5-7]

MATERIALS AND METHODS

This study was conducted for seven months, from May 2023 to December 2023. A total of 18 male albino Wistar rats *(Rattus norvegicus)* with a body weight (BW) of 275-300 grams and age of two to three months were obtained from the experimental animal development unit at Universitas Gadjah Mada. They were made into incisional hernia models within 14 days. Furthermore, the subjects were divided into three groups with different defect closure method using free omental patch (FOP), polypropylene mesh plus free omental patch (FOP-PPM), and composite mesh (CM). The polypropylene mesh PPM used in this study was a polypropylene knitted mesh, which was non-absorbable, light weight, large pore (1.3 x 1.1 mm), thickness 0.43 mm, and burst strength 585 kPa. The CM used in this study was a macroporous, partially absorbable, tissue-separating mesh, combining large-pore mesh knitted with monofilament fibers and natural absorbable tissue separating technology. Abdominal wall wound was excised using Metzenbaum and the sample was taken from 3 separated site from it to see the expression of qPCR of VEGF, COL3A1, COL1A1, and COL1A2 after 21th day. This study has received approval from The

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Table I: Expression of VEGF and collagen in the usage of Polypropylene Mesh-Free Omental Patch (PPM-FOP) compared to Composite Mesh (CM)

	PPM – FOP		CM		p-value
	Average	SD	Average	SD	
VEGF	0.09	0.125	0.217	0.254	0.79
COL3A1	1.34	1.607	2.22	2.236	0.96
COL1A1	1.29	1.256	1.52	0.965	0.98
COL1A2	0.10	0.125	0.22	0.254	0.77
COL1A1/COL3A1	1.02	1.281	1.46	2.317	0.08

Table II: Expression of VEGF and Collagen in the usage of Free Omental Patch (FOP) compared to Composite Mesh (CM)

	FOP		CM		p-value
	Average	SD	Average	SD	
VEGF	0.066	0.076	0.217	0.254	0.315
COL3A1	1.3	1.658	2.22	2.236	0.898
COL1A1	0.95	0.895	1.52	0.965	0.558
COL1A2	0.067	0.076	0.22	0.254	0.315
COL1A1/COL3A1	1.36	1.862	1.46	2.31	0.187

Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Gadjah Mada University with the Ethical Clearance number: KE/FK/1174/EC/2023 and animal welfare.

Incisional hernia model

All subjects were sedated using diazepam 25 mg/kgBW and ketamine 2.5 mg/kgBW. The abdominal region was prepared and shaved. Aseptic procedure was performed using povidone iodine followed by 2 cm of median incision until the fascia and peritoneum (Figure 1). Fascia was left opened and the skin was sutured using a monofilament non-absorbable suture 4.0. After 14 days, the hernia incisional model was successfully obtained (Figure 2).

Defect closure

A 2 cm of abdominal incision was performed at the lateral side of the incisional hernia until fascia and peritoneum. The defect was identified and closed with FOP, FOP plus PPM, and CM by sublay method at the preperitoneal space. The fixation was using running suture with multifilament absorbable 4.0. The abdominoplasty was performed using monofilament non-absorbable 4.0 with simple continuous running suture.

Statistical analysis

The analysis was performed with SPSS 23 on Microsoft Windows 11. Normality test was assessed using the Shapiro-Wilk test. Student t-test was performed to compared the expression of VEGF, COL3A1, COL1A1, COL1A2 and COL1A1/ COL3A1 ratio, between FOP, FOP-PPM, and CM all at a 95% confidence level.

RESULTS

All 18 test subjects underwent all stage of the test, from the make of hernia model, hernia closure, until termination and the qPCR test of the abdominal wall tissue. No dead, infected, nor ill subject during the study. The experimental results are shown in Table I and Table II.

As shown in Table I and Table II in the terms of VEGF expression, there were no difference in the usage of FOP-PPM compared to the CM with the p-value of 0.79 ($p>0.05$), nor between the FOP alone compared to the CM with the p-value of 0.315 ($p>0.05$). Similar results showed in Collagen expression, where there was no difference in the usage of FOP-PPM compared to the CM in all the Collagen type tested, COL3A1, COL1A1, and COL1A2 with the p-value of 0.96, 0.98, and 0.77 ($p>0.05$) respectively, nor between the FOP alone compared to the CM with the p-value of 0.898, 0.558, and 0.315 ($p>0.05$) respectively. In addition, there was also no significant difference of COL1A1/ COL3A1 ratio either between the FOP compared to the CM, or FOP-PPM compared to the CM.

DISCUSSION

Incisional hernia can be repaired by various procedure. Direct closure using Mayo technique can be used to close the defect. However, the recurrence percentage is high and can only be applied for small defect.[9] Defect closure using mesh can be performed for larger defect with less recurrence. However, the using of mesh, especially PPM can promote intraabdominal adhesion. CM is the current "gold standard" for defect closure of incisional hernia due to its "biface implants" with a porous external surface to encourage tissue integration and a smooth microporous internal surface to prevent adhesions when placed in contact with viscera.[10] However, CM is relatively high in price and not widely available in developing countries.

The utilization of PPM plus fresh amniotic sac for the closure of hernia defects in rats demonstrated noteworthy outcomes in the mitigation of the risk of adhesions. This was achieved by reducing postoperative inflammation and enhancing the

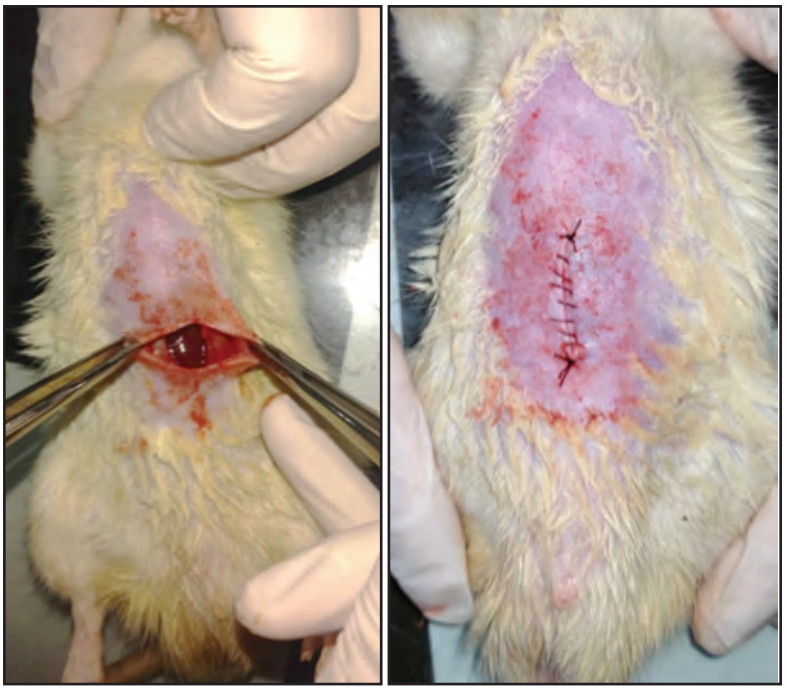

Fig. 1: Midline incision for hernia model

Fig. 2: Hernia incisional model after the 14th day

epithelialization process, which is a crucial step in the wound healing cascade. In the context of this study, PPM plus FOP demonstrated its ability to be equivalent to CM in accelerating wound healing. This was evidenced through the increased expression of several key biomarkers, including VEGF, COL3A1, COL1A1, COL1A2 and COL1A1/ COL3A1 ratio, which all play important roles in the process of tissue regeneration.[11]

Vascular endothelial growth factor (VEGF) is crucial for angiogenesis, the process of new blood vessel formation, which is essential for delivering nutrients and oxygen to healing tissues. VEGF drives several steps in the angiogenic cascade, including the migration and proliferation of endothelial cells, which are vital for forming new blood vessels at the wound site. This process enhances tissue perfusion, facilitating better healing outcomes. VEGF also stimulates the deposition of collagen types I and II, as well as

epithelial cell migration, contributing to structural integrity and wound closure.[12]

Collagen type III alpha 1 (COL3A1) plays a significant role in the context of hernia repair, particularly in understanding the mechanisms underlying hernia formation and recurrence. An imbalance between collagen types I and III is a critical factor in the mechanical stability of connective tissue. A decreased ratio of type I to type III collagen (COL1A1/ COL3A1 ratio) has been observed in patients with inguinal and incisional hernias, which may lead to mesh instability and increased hernia recurrence rates. This imbalance arises from an increase in immature type III collagen, which is mechanically less stable than mature type I collagen.[13]

The combination of hernia mesh and omentum has been demonstrated to markedly enhance the safety and efficacy of hernia repair. The placement of the omentum between the visceral and polypropylene mesh can effectively prevent complications associated with direct contact between the mesh and internal tissues, such as adhesion and infection. This approach not only reduces the risk of mesh-related problems, but also contributes to better repair outcomes. Furthermore, the use of the omentum in hernia repair has been associated with reduced recurrence rates and postoperative complications, especially in complex hernia cases and emergency situations where a quick and effective repair is essential.[14]

The findings of this study indicate that both defect closure using FOP and MPP-FOP exhibit comparable efficacy to MC in the context of wound healing. This was demonstrated through the non-significant different in the expression of VEGF, COL3A1, COL1A1, COL1A2, and COL1A1/COL3A1 ratio between those treatment option. These findings confirm the potential use of FOP, either alone or combined with PPM, as an effective alternative in incisional hernia defect closure surgery.[15]

The limitation of this study was that only one side of the abdominal wall was harvested. We just harvest the abdominal wall once, three weeks after defect closure then sacrifice the rats. We only use 2 meshes type: PPM and CM. This study focuses on wound healing process, we did not measure the tensile strength and biomechanical of hernia mesh.

CONCLUSION

In this study, it was found that both FOP and FOP-PPM exhibit comparable effectiveness to MC in wound healing. This was demonstrated through the non-significant different in the expression of VEGF, COL3A1, COL1A1, COL1A2, and COL1A1/COL3A1 ratio between those treatment option. These findings confirm the potential use of FOP, either alone or combined with PPM, as an effective alternative in incisional hernia defect closure surgery.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Usability and functionality of M-DFEET application for the independence of foot care in diabetes mellitus patients

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ABSTRACT

Introduction: Diabetes mellitus (DM) poses significant challenges in foot care management, often leading to severe complications if not properly addressed. Diabetic Peripheral Neuropathy (PND) is commonly associated with diabetic foot ulcer (DFU) and is a leading cause of hospital admissions and prolonged treatment durations. Therefore, this study aimed to determine the usability and functionality of the Mobile Diabetic Foot Early Self-Assessment (M-DFEET) application for the independence of foot care for DM patients in the South Denpasar Community Health Centre area.

Materials and Methods: This is a cross-sectional study with 60 DM patients, selected by simple random sampling. The instrument used consists of the DM patient observation sheet-based user view and the M-DFEET application. Categorical data were classified as frequency and percentage, while the numerical data were reported as mean and standard deviation (SD).

Results: The evaluation results show that all 60 participants (100%) rated the functionality of the M-DFEET application as excellent in helping with foot care. Furthermore, most participants, 55 (91.7%), assessed the efficiency of the application as good. Regarding the usability, 58 participants (96.7%) considered it good, while the remaining participants deemed it adequate. These findings underscore the application's potential to optimize time and effort for its users effectively.

Conclusions: The feedback on the M-DFEET application is overwhelmingly positive, with all participants rating its functionality as very good for foot care. The application is likely to be well-received by users especially T2DM patients, and holds potential as an evaluative tool in foot care management.

KEYWORDS:
Diabetes mellitus, foot care, functionality, M-DFEET, usability

INTRODUCTION

Diabetes mellitus (DM), often referred to as a silent killer, is associated with serious long-term complications.[1] It represents a significant global public health challenge and is one of the leading causes of mortality worldwide.[2,3] Among the most severe complications of DM is Diabetic Peripheral Neuropathy (DPN), a condition that significantly increases the risk of developing Diabetic Foot Ulcers (DFU). In addition to being a major cause of prolonged hospital stays.[4,5] DFU contributes to increased healthcare costs, higher disability rates, diminished quality of life, and an elevated risk of mortality.

DFU is one of the most preventable long-term complications of diabetes. Prevention is supported by five key elements: 1) identifying feet at risk, 2) regular inspection of feet at risk, 3) educating patients, family members, and healthcare providers; 4) ensuring proper footwear use, and 5) managing risk factors.[6] These five elements are important for preventing DFU, amputation, and maintaining the quality of life of patients. Diabetic foot is a severe consequence of chronic DM, characterized by deep tissue lesions associated with neurological impairments and peripheral vascular disease of the lower extremities.[7]

The increasing incidence of diabetic foot disease is closely linked to the global increase in DM prevalence and the prolonged life expectancy of patients. The prevalence of DFU in T2DM is relatively high, with most patients having lived with the condition for over a decade. Approximately 60% of these patients experience impairments, including a significant risk of leg amputation.[6,8] The risk of amputation occurs every 30 seconds and is 15-40 times more frequent in DM patients compared to non-DM patients. Furthermore, 85% of amputations in DM patients begin with foot ulceration, which often progresses to gangrene or severe infection.[3,8,9] Considering these alarming statistics, increasing awareness of DFU problems is very important. The challenges posed by this condition include increasing incidences of foot complications, extended waiting times for treatment, and difficulties in early detection. These issues underscore the need for creative, innovative, and effective solutions that patients can utilize independently. One such solution is by making an application that can facilitate families and DM patients to carry out foot examinations independently at home (M-DFEET Application, available at https://denpasarinstitute.com/M-DFEET_1_1.0.apk).[10,11]

This Android-based Mobile Diabetic Foot Early Self-Assessment (M-DFEET) application is designed using the "Inlow's 60-second diabetic foot screen tool" as its foundation.[12] The application includes a login menu, a main menu with patient information, a diabetes screening form, foot assessment items (visual, touch, sensation), early foot assessment results, recommendations, health education, and notifications. The visual evaluation included assessing the

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Table I: Characteristics of Research Participants (n = 60)

Characteristics		n	%
Age (year)	36-45	20	33,3
	46-55	16	26,7
	>55	24	40
Gender	Female	34	56,7
	Male	26	43,3
Duration of DM	< 5 years	50	83,3
	>5 years	10	16,7

Table II: Evaluate the patient's ability to use the M-FEET application (n = 60)

Variables	Category		
	Good n (%)	Enough n (%)	Not enough n (%)
Q1 Login capability	50 (83.3)	10 (16.7)	0 (0)
Q2 Identity filling capability	54 (90)	6 (10)	0 (0)
Q3 Confidence instrument filling capability	45 (75)	15 (25)	0 (0)
Q4 Capability of filling instruments for early detection of diabetic feet	53 (88.3)	7 (11.7)	0 (0)
Q5 Ability to understand the parameters and conclusions of early detection examination scores for diabetic feet	50 (83.3)	10 (16.7)	0 (0)
Q6 Ability to understand recommendations based on foot examination results	58 (96.7)	2 (3.3)	0 (0)

Table III: Evaluate patient opinions in using the M-DFEET application (n = 60)

Rated Aspect	Category			Score Mean (SD)
	Good n (%)	Enough n (%)	Not enough n (%)	
Functionality	60 (100)	0 (0)	0 (0)	33.95 (2.587)
Efficiency	55 (91.7)	5 (8.3)	0 (0)	45.58 (4.637)
Usability	58 (96.7)	2 (3.3)	0 (0)	44.90 (4.181)

foot's skin, toenails, deformity pressure, and footwear. The touch was used to assess skin temperature and detect pedal pulses, while sensation was assessed using a cotton tip. The quality of this application is also based on an assessment from the user's perspective such as functionality, reliability, efficiency, usability, and portability. However, the functionality and usability of this application still need to be tested on DM patients.[13] Therefore, this study aimed to investigate the usability and functionality of the M-DFEET application in promoting independent foot care for DM patients.

MATERIALS AND METHODS

This cross-sectional study focusing on the usability and functionality of an Android-based independent foot care application called M-DFEET application for DM patients was carried out from April to May 2023. This application contains patient information, a diabetes screening form, foot assessment items (visual, touch, sensation), early foot assessment results, recommendations, and health education. The NBR ISO/IEC 9126-1, a standard issued by the International Organization of Standardization and the International Electrotechnical Commission and later amended and translated by the Brazilian Association of Technical Standards was adopted. This standard defines a quality model for software products from two perspectives, including internal and external quality,[14] which consists of a set of properties to fulfill the user's demands, such as functionality, usability, dependability, efficiency, maintainability, and portability.

The four qualities that define a usable quality are effectiveness, productivity, safety, and satisfaction. Usability focuses on evaluating the finished product from the user's perspective, measured by the performance attained by the target audience when using the program. In this context, software is considered usable when it is intelligible, comprehensible, and operable making it simple enough for the users to grasp, learn, and use. High usability is crucial to software success since it allows users to use the application's capabilities and resources quickly and efficiently. On the other hand, functionality refers to the application's ability to provide operations and tools to meet users' demands.

Participants

The DanielSoper independent sample size calculator determined that sixty beta testers were sufficient to evaluate the usability and functionality of this mobile application. The participants consisted of DM patients from South Denpasar Health Centre. The total number of beta testers was selected due to study findings suggesting that 10 participants in the usability test would detect 94.7% of all usability issues.[15,16] The participants were recruited using a simple

random sampling method from among T2DM patients. Eligibility criteria included having either a history of DM for more than five years or a diagnosis within the past six months accompanied by symptoms, particularly neuropathic disorders. Participants were also required to have an Android device, such as a smartphone or tablet.

Materials
In this study, the instrument used was an observation sheet-based user view to evaluate the patient's ability to use the M-DFEET application and the patient's opinion regarding the application. The abilities assessed include log-in, fill-in identity, features about trust instruments, features about early detection of diabetic feet, features about parameters and conclusions about early detection of diabetic foot examination scores, and understanding recommendations. An opinion evaluation includes functionality, efficiency, and usability.

Procedures
Participants were first instructed to install the M-DFEET application on their respective Android devices. Once installed, they were asked to use the application for two months. After this period, participants provided feedback on the user interface, focusing on its usefulness, functionality in providing warnings, and effectiveness in early detection of diabetic foot conditions.

Statistical analysis
The data was entered and analyzed using IBM SPSS Statistics Version 24. Subsequently, categorical data were presented in frequencies and percentages, whilst numerical data were presented as mean and standard deviation (SD).

Ethical statement
The ethical clearance of this study was obtained from the health research ethics commission of the Institute of Technology and Health Bali with the protocol number: 04.0295/KEPITEKES-BALI/IV/2023. Participants provided written informed consent after being thoroughly briefed on the aim of this study.

RESULTS

Respondent characteristics
Most of the participants were over 55 years old (40%), of female gender (56.7%), and had suffered from DM for <5 years (83.3%).

Evaluation of T2DM patient's ability to use the M-DFEET application
The success of implementing the Android-based M-DFEET application was evaluated using an observation sheet. The results showed that the majority of 50 participants (83.3%) have good abilities when logging in to the M-DFEET application. However, 10 (16.7%) participants had a good ability to log in to the M-DFEET application. Most participants, 54 (90%), had good abilities in filling in personal identity features. Most participants, 45 (75%), were able to understand features about confidence instruments, 53 (88.3%) understood features about early detection of diabetic feet, and 50 (83.3%) understood features about parameters and conclusions of examination scores for early detection of diabetic feet. Most participants, 58 (96.7%) also had good abilities in understanding recommendations based on the results of foot examinations.

Evaluate the opinions of T2DM patients when using the M-DFEET application.
The success of implementing the Android-based M-DFEET application was also evaluated through patient feedback, measured using an observation sheet. All 60 participants (100%) reported that the M-DFEET application functioned very well in supporting foot care. Most participants (55, 91.7%) rated the application's efficiency as good, while five participants (8.3%) found it satisfactory. Regarding usability, 58 participants (96.7%) rated it as good, while the remaining two participants considered it satisfactory.

DISCUSSION

The M-DFEET application was developed as an early screening tool to prevent diabetic foot problems and has been validated as a reliable and trustworthy resource.[17] Designed with the specific needs of T2DM patients in mind, the application enables users to perform foot inspections independently, at their convenience, and from any location.[10] The M-DFEET application also assesses the patient's confidence in carrying out routine and autonomous foot examinations. This study used the Health Belief Model (HBM) theoretical approach, which is the most extensively used theory to explain health behaviour.[18] This theory describes how a perceived or individual belief in sickness influences health behaviour. The HBM suggests that an individual's perceived susceptibility to illness, its severity, and the perceived benefits and barriers to action influence health behavior. Individuals who perceive a higher risk of severe disease complications are more likely to take appropriate health measures. The chosen course of action is typically the one offering the greatest benefits with the least resistance or difficulty. Health behaviors, such as the early diagnosis of diabetic foot conditions, are motivated by internal and/or external cues to action.[19]

The quality of the produced application is determined by the user's perception of its usefulness, dependability, efficiency, usability, and portability.[20] A trial application of the development of an Android application-based early detection instrument for diabetic feet was carried out on 60 DM patients. In line with M-DFEET application usability testing, this study showed that 100% of the participants considered the mobile application easy to use. A user-friendly mobile application such as M-DEET encourages adoption even among those who are unfamiliar with it or have no immediate.[21] All participants unanimously agreed that the different functionalities of the M-DFEET application were nicely integrated. In the modern era, a single mobile application was expected to perform several functions in order to accelerate access to information. Additionally, using a single mobile application to access multiple features is more time-efficient than relying on several separate applications. The universal ease of use reported by participants can be attributed to M-DFEET's familiar and consistent design, which simplifies navigation and functionality.

All participants were found to have good understanding and skill in using the Android-based application developed for early detection of diabetic foot. After the activity of familiarizing with the application was completed, its reliability and trustworthiness was established by getting Type 2 diabetes (T2DM) patients to conduct their own foot examination using this Android application.[22] The process included instructions on how to download the application, log in, fill out the application, and interpret the results and recommendations according to the scheduled timeline. To ensure that the application meets its objectives and provides clinical benefits, patient comprehension was evaluated through behavioral changes in self-care practices, such as an increased frequency of foot exams, more consistent foot hygiene routines, and adherence to clothing recommendations. Direct observations by researchers over the course of two months of data collection showed no diabetic foot problems, such as ulcers or infections, as well as an improvement in overall foot health. However, some participants often face challenges in accessing the application due to internet network costs, especially for those who live in remote areas.

M-DFEET application offers a cost-effective alternative to in-person clinical examinations by reducing the need for frequent clinic visits. The application is free, ensuring accessibility for a wide range of users, particularly in resource-limited settings. Its availability anytime and anywhere enables patients to monitor their foot health without scheduling clinic appointments. This feature is particularly beneficial for individuals in remote areas or those with This feature is especially advantageous for individuals in remote areas or those with limited mobility, as it helps eliminate barriers to care. To identify risk factors and symptoms of diabetic foot issues, M-DFEET application uses evidence-based questionnaires. Key questions include: Do you experience pain, tingling, or numbness in your feet? Have you noticed any sores or changes in the temperature or color of your skin? Do you regularly examine your feet for sores? Additionally, the application integrates advanced features, such as image analysis and symptom tracking, to improve diagnostic accuracy. Based on user responses, the application categorizes individuals into low-, medium-, or high-risk groups, providing tailored recommendations. For instance, low-risk users receive preventive care tips, while high-risk users are advised to seek immediate clinical evaluation. By promoting self-management and patient education, the M-DFEET application empowers users to take proactive steps, facilitating early intervention and reducing the risk of complications.

Developing effective applications requires a strong emphasis on validity to ensure they accurately measure the intended outcomes.[14,16] This process involves aligning the application's content with the study objectives while maintaining relevance to the target population.[13] In this regard, precise operational definitions play a critical role to guide the design of the application to ensure that it can capture the variations among users effectively. For example, in this study, the application should be able to differentiate different individuals (e.g. patient with high risk versus those with low risk) based on the responses they enter into the application.

When designing instruments for mobile applications such as the M-DFEET application, usability is another key consideration to optimize functionality and enhance the user experience. Clear and concise questions tailored to the target population are essential for gathering reliable data. Understanding how users interact with the application will further enhance its continuous improvement and effectiveness in both clinical and non-clinical settings.

Reliability is crucial in ensuring consistent results across repeated assessments. For example, the M-DFEET application has been adapted to meet the needs of T2DM patients and tested for reliability.[10] The application has shown potential for integration into existing healthcare services, enabling early detection of diabetic foot issues and supporting preventive care strategies. Future enhancements to the M-DFEET application could include features such as personalized foot care guidance for DM patients. Additionally, further study is needed to assess the long-term impact of M-DFEET application on patient behavior and its effectiveness in preventing diabetic foot ulcers. These studies should include larger, more diverse populations and extended follow-up periods to provide comprehensive evidence of the application's benefits.

CONCLUSION

application is specifically designed to assist users, especially individuals with T2DM, in performing foot examinations independently, anytime, and anywhere, thereby eliminating the need for frequent visits to healthcare facilities. By prioritizing user accessibility and ease of use, the application empowers patients to take a proactive role in managing their foot health. The M-DFEET application incorporates patient-centered features and is supported by a theoretical framework building confidence in early detection and routine, independent foot care. This approach enables T2DM patients to monitor their foot health effectively while enhancing their self-efficacy in preventing complications. The implementation of the M-DFEET application has the potential to advance evidence-based nursing practices by significantly reducing disability and mortality associated with diabetic foot complications. By focusing on early intervention and preventive care, the M-DFEET application contributes to better clinical outcomes and improved patient quality of life.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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The mediating effect of mental health status between self-system and sexual risk behaviour among university students in Malaysia

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ABSTRACT

Introduction: Young adults' engagement in sexual risk behaviour (SRB) is a growing concern worldwide. Addressing this issue is crucial as it can lead to various detrimental effects on individuals, including psychological, behavioural, and, in severe cases, suicidal tendencies and mortality. This nationwide study aimed to determine the mediating roles of depressive, anxiety, and stress symptoms in the relationship between adverse childhood experiences (ACE), religiosity, knowledge on sexuality, attitude towards premarital sex, and SRB among young Malaysian adults using structural equation modelling (SEM).

Materials and Methods: A quantitative, cross-sectional design was employed in this study. Respondents were recruited from June to December 2021 among students attending higher education institutions in Malaysia. Institutions were sampled using stratified random sampling and the respondents were selected via convenience sampling. Data were collected via an online survey that inquired about respondents' socio-demographic characteristics, ACE, religiosity, knowledge on sexuality, attitude towards premarital sex, mental health status (MHS), and engagement in SRB. The data were analysed using SPSS version 27 for descriptive analysis, and SPSS AMOS version 27 for structural equation modelling (SEM) analysis.

Results: A total of 1171 respondents were recruited in this study. From the SEM analysis, the proposed model indicated a good fit, and it explained 26% of the SRB variance. There was a partial mediation effect of the relationship between ACE on SRB through MHS ($p<0.05$), as well as religiosity on SRB through MHS ($p<0.05$). There was no significant mediation effect was found for the other variables.

Conclusion: This study highlighted the mediation effect of MHS between ACE on SRB, as well as between religiosity and SRB. Apart from addressing ACE and religiosity of the young adults, MHS should also need to be explored when dealing with SRB issues and vice versa. Preventive measures should be considered at younger stage to prevent high risk behaviour among young adults.

KEYWORDS:
Sexual risk behaviour, mental health, adverse childhood experiences, religiosity

INTRODUCTION

Young adults are vulnerable to engaging in risky behaviours, including sexual risk behaviour (SRB). SRB is imperative to address as it can lead to various reproductive health problems and psychological issues.[1] SRB is defined as engagement in premarital sex, early sexual debut, and having multiple sexual partners.[2,3] Malaysia has reported an increase from 7.3% to 7.6% between 2017 and 2022.[4,5] Nonetheless, Malaysia still ranks among the countries with the lowest reported rates of engaging in SRB.

The escalation of mental health issues among young adults, particularly those in tertiary education, is a growing concern with wide-ranging consequences.[6,7] Depression, anxiety, and stress are among commonly experienced by tertiary level students.[8] Studies have shown that poor mental health status (MHS) could lead to engagement in SRB.[9]

In addition, depression, anxiety, and stress, are often associated with adverse childhood experiences (ACE), religiosity, knowledge of sexuality, and attitudes toward premarital sex among young adults. It has been reported that individuals who have experienced adversities during childhood are more likely to engage in SRB.[10] Studies have also highlighted that those who exhibit high engagement in religiosity are associated with lower rates of SRB, as religious beliefs often influence moral standards, thus discouraging such behaviours.[11] Similarly, individuals with permissive attitudes toward premarital sex tend to engage in fewer SRBs, as they adhere to conservative sexual practices and norms.[12]

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Additionally, a limited understanding of sexual health often leads to an increased SRB, as individuals may lack the necessary knowledge for informed decision-making.[13] These factors collectively highlight the determinants contributing to SRB among young adults.

Furthermore, psychological factors such as depression, anxiety, and stress can significantly increase the likelihood of engaging in SRB. Studies have consistently found that individuals commonly report experiencing anxiety symptoms, followed by depressive and stress symptoms.[6] The severity of mental health symptoms correlates positively with the likelihood of engaging in SRB.[9,14] Emotional instability can result in emotionally driven decision-making, leading to involvement in risky behaviours.[9] Therefore, this study aims to employ the Problem-Behaviour Theory (PBT) proposed by Jessor & Jessor to understand the underlying mechanisms of SRB.[15] Specifically, the mediating effect of MHS between ACE, religiosity, knowledge on sexuality, and attitude towards premarital sex, and SRB.

MATERIALS AND METHODS

Study design and setting

This study adopts a quantitative, cross-sectional design conducted among young Malaysian adults attending tertiary education institutions in Malaysia. Data collection was carried out from June to December 2021.

Study population

The study recruited students who were in the young adult category, from tertiary education institutions in Malaysia, specifically Malaysian citizens aged 18-24 years, proficient in either Malay or English. Individuals diagnosed with psychiatric illness were excluded to prevent bias in responding to the Depression Anxiety Stress Scale-21 (DASS-21), which screens for mental illness. The sample size was determined using the Daniel-Sopher Sample Size Calculation for Structural Equation Model. Considering a significance level of 0.05, anticipated effect size of 0.2, statistical power of 0.8, along with the inclusion of 34 manifest variables and seven latent variables, the recommended minimum sample size was 425. Following adjustment for a 70% non-response rate, the final minimum sample size was determined to be 723 respondents.

Sampling method

A two-stage sampling method was employed, with institutions chosen through stratified random sampling, and students were selected via convenience sampling. Malaysia was stratified into Peninsular Malaysia and East Malaysia, with Peninsular Malaysia was further divided into five regions for sampling. Gatekeepers from each selected institution distributed the survey link through official WhatsApp groups and emails. Students who volunteered responded to the survey. Sample size in each region were determined proportionally to the number of students. Out of 32 selected institutions, only 25 institutions agreed to participate in the study.

Study instrument

A self-administered online questionnaire consisting of seven sections was used, with the first section comprising the informed consent form. The second section contained questions related to socio-demographic characteristics of the respondents. The subsequent sections covered ACEs, religiosity, knowledge on sexuality, attitude towards premarital sex, MHS, and SRB. All instructions and questions were available in both English and Malay to facilitate respondents' comprehension.

A history of ACE was assessed using a set of dichotomous questions focusing on four major forms of ACE which are childhood sexual abuse, physical abuse, emotional abuse, and neglect. This scale showed an acceptable level of internal consistency, with a Cronbach's alpha value of 0.61. Face validity was tested to ensure the instrument measured what it is intended to measure. Total scores ranged from 0-4, with higher scores indicating a history of multiple exposures to ACE.

The Duke University Religion Index (DUREL) was utilized to assess the respondents' level of religious involvement.[16] The DUREL exhibits high test–retest reliability (intra-class correlation=0.91), internal consistency (Cronbach's alpha=0.78–0.91), and convergent validity with other religiosity measures (r=0.71–0.86). Similarly, the Malay-translated version (DUREL-M) also demonstrates a good internal reliability of 0.8.[17] It comprises of a Likert scale with five items, measuring three dimensions: organizational religious activity (ORA), non-organizational religious activity (NORA), and intrinsic religiosity (IR). ORA involves religious activities conducted in formal and public settings, while NORA refers to private religious activities. IR reflects the internal dimension such as engaging in religious activities as an ultimate goal. Scores on the DUREL range from 5 to 27, with higher scores indicating greater religiosity.

A set of questionnaire on fundamental knowledge of sexuality was adopted from a prior study conducted by Nik Farid et al. (2013).[18] These questionnaires demonstrate a moderate kappa value of 0.41. The questionnaire comprises six items related to knowledge on sexuality, including inquiries such as "A person can get pregnant after having sexual intercourse once", "Have you ever heard of contraception?", "Which of the following are types of contraception?", "Do you know about sexually transmitted infections?", "Which of the following are sexually transmitted infections?", "From the list below, which of the following are symptoms of sexually transmitted infections?". The total score ranges from 0 to 17 and categorised into two, inadequate and adequate knowledge of sexuality. The cut-off point was set using the mean score value, which was 10.

Respondents' attitude towards premarital sex were assessed using questions adopted from a prior study conducted by Nik Farid et al. (2013).[18] This adopted questionnaire has an excellent Cronbach's alpha of 0.85. The questions consisted of four items with a 4-point Likert scale. The questions were "It is alright for people my age to have sex before marriage if both people want to", "It is okay for people my age to have sexual intercourse as long as they have fallen in love", "Having sexual intercourse before marriage is not a good choice, but I can understand it" and "Young people who have premarital sex should be punished". The last question was reverse coded. The sum of the scores ranging from 1-16, and

higher scores indicates a high level of non-permissiveness towards premarital sex.

The Depression, Anxiety and Stress Scale (DASS-21) developed by Lovibond and Lovibond (1995) was employed to evaluate three domains of MHS: depression, anxiety and stress. The depression domain assesses feelings of hopelessness, devaluation of life, anhedonia, and lack of interest.[19] The anxiety domain evaluates autonomic arousal, skeletal muscle effects, situational anxiety, and the presence of anxious feelings. The stress domain measures chronic, and non-overreactive arousal. demonstrated high internal consistency, with Cronbach's alpha values of 0.91 for the depression domain, 0.84 for the anxiety domain, and 0.90 for the stress domain.[19] Similarly, the translated Malay version exhibited Cronbach's alpha values of 0.84 for the depression domain, 0.74 for the anxiety domain, and 0.79 for the stress domain.[20] It employs a 4-point Likert scale, and the sum score is calculated separately for each domain. Subsequently, the total score is doubled and classified into five levels of severity: normal, mild, moderate, severe, and extremely severe. The scores were further categorised into normal and abnormal (mild to extremely severe) using cut-off scores of ≤9 for a normal depressive symptom, ≤7 for anxiety, and ≤14 for stress symptoms.

Respondents' engagement towards SRB was determined using an adopted from a previous study by Nik Farid.[21] It demonstrated a Cronbach's alpha reliability coefficient of 0.85. The questionnaire comprised dichotomous questions, with the first question determining whether respondents had ever engaged in sexual activity. Subsequently, four follow-up questions were presented if respondents responded 'yes' and were scored as '1' indicating their engagement in SRB. Respondents who responded negatively were scored as '0', indicating no engagement in SRB. The total score of SRB ranges from zero to five and respondents that scored "Yes" to any of the items would be considered as engaging SRB.

Data collection

Data collection was facilitated by the Student Representative Council and Student Affairs Department, serving as gatekeepers within each institution. These gatekeepers distributed a link containing the informed consent form via email and WhatsApp to the targeted respondents. Subsequently, respondents who met the inclusion criteria were granted access to the questionnaire. To ensure genuine responses without concerns of criticism or judgment, the surveys were conducted anonymously and confidentially, thereby reducing social desirability bias.

Data analysis

Data were managed and analysed using SPSS version 27, with Statistical Package for Social Sciences (SPSS) AMOS version 27 utilized specifically for analysing the mediation effect. The dataset was cleaned to identify missing values, coding errors, or illogical values. Descriptive statistics were computed for all variables. Categorical data were reported as frequencies and percentages, and continuous data as median and interquartile range (IQR) as these were found to be not normally distributed data. Goodness of fit was measured using Chi-Square (Chisq), the Root Mean Square Error of Approximation (RMSEA), and the Goodness-of-Fit Index (GFI); Incremental Fit, which includes the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Normed Fit Index (NFI), were also employed to evaluate the model fit. The mediation effect was assessed using bootstrap analysis methods which utilised the resampling technique. In this study, the resampling number was set at 5000.

Ethical approval

Ethical clearance was granted by the Medical Research and Ethics Committee for Research Involving Human Subjects at Universiti Putra Malaysia (approval ID: JKEUPM-2021-141). he acquired data were treated with confidentiality and will be securely disposed off after a period of 5 years. Respondents who exhibited severe or extremely severe symptoms in the DASS-21 domains were contacted for additional assessment upon their consent.

RESULTS

Table I outlined the demographic characteristics of the respondents. Majority of the students aged between 18-20 years (60.3%, n=706), females (70%, n=820), Malays (62.3%, 730), Muslims (66.5%, 779), living in urban areas (65.8%, n=770), staying with family (89.2%, n=1044), currently single (99.7%, n=0.3), parents were still married (84.4%, 988), household income below RM4,849 (58.5%, n=685). In terms of academic background, studying at public institutions (n=50.3, n=589), pursuing social science stream (61.7%, n=722), in their first year of tertiary study (45.3%, n=531).

As of MHS, most of the respondents reported having normal depressive symptoms (54.4%, n=637), abnormal anxiety symptoms (60.5%, n=709), and normal symptoms of stress (68.5%, n=802). Stress symptoms reported to have the highest median score of 12.0 (IQR=14) followed by anxiety, and stress. Additionally, there was a fraction (7.2%, n=84) of the respondents reported engaging in SRB. Table II present the summary of young adults' engagement in SRB.

Among four forms of ACE, most of the students reported experiencing history of childhood emotional abuse (11.4%, n=133), child neglect (4.3%, n=50), physical abuse (3.8%, n=44), and sexual abuse (2.7%, n=32). Overall, the ACE median score was 0.0 (IQR=0) indicating limited variability in the total scores among the respondents. IR scored the highest median score, followed by ORA, and NORA with median score of 14.0 (IQR=4.0), 6.0 (IQR=3.0), 5.0 (IQR=4.0), respectively. Overall, the respondents showed a high engagement in religiosity with a median score of 25.0 (IQR=10.0). The distribution of knowledge on sexual health among the respondents were almost equal where 594 (50.7%) of the students reported having an adequate knowledge on sexuality, while 577 of the respondents reported having inadequate knowledge on sexuality (49.3%). The overall median score for knowledge on sexuality was 11.0 with interquartile range of 5.0. Furthermore, half of the respondents admitted to being non-permissive towards premarital sex (50.7%, n=674) than being permissive towards premarital sex (42.4%, n=497). The overall median score was 13.0 with an interquartile range of 6.0. Table III presents the detailed breakdown of the studied factors.

Table I: The sociodemographic characteristics of the respondents (N=1171)

Variables	n	%
Age		
18-20 years old	706	60.3
21-24 years old	465	39.7
Gender		
Male	351	30.0
Female	820	70.0
Race		
Malay	730	62.3
Non-Malay	441	37.7
Religion		
Muslim	779	66.5
Non-Muslim	392	33.5
Locality		
Rural	401	34.2
Urban	770	65.8
Living arrangements		
With family	1044	89.2
Without family	127	10.8
Current relationship status		
Single/in a relationship	1168	99.7
Married	3	0.3
Parents' marital status		
Married	988	84.4
Others	183	15.6
Household income		
<RM4,849	685	58.5
RM4,850 – RM10,959	357	30.5
>RM10,960	129	11.0
Academic background		
Institution		
Public	589	50.3
Private	582	49.7
Field of study		
Science	449	38.3
Social Science	722	61.7
Year of study		
Year 1	531	45.3
Year 2	307	26.2
Year 3	228	19.5
Year 4	105	9.0

Table II: The prevalence of mental health status and sexual risk behavior among the respondents (N=1171)

Variables	n	%	Median	IQR
Depressive symptoms				
Normal	637	54.4	8.0	14
Abnormal	534	45.6		
Anxiety symptoms				
Normal	462	39.5	10.0	14
Abnormal	709	60.5		
Stress symptoms				
Normal	802	68.5	12.0	14
Abnormal	369	31.5		
Sexual Risk Behavior (SRB)				
SRB	84	7.2		
Non-SRB	1087	92.8		

Table III: The prevalence of the adverse childhood experiences, religiosity, knowledge on sexuality, and attitude towards premarital sex (N=1711)

Variables	F	%	Median	IQR
Adverse Childhood Experiences			0.0	0
History of sexual abuse				
No	1139	97.3		
Yes	32	2.7		
History of physical abuse				
No	1127	96.2		
Yes	44	3.8		
History of emotional abuse				
No	1038	88.6		
Yes	133	11.4		
History of child neglect				
No	1121	95.7		
Yes	50	4.3		
Religiosity			25.0	10.0
Organized religious activity (ORA)			6.0	3.0
Non-organized religious activity (NORA)			5.0	4.0
Intrinsic religiosity (IR)			14.0	4.0
Knowledge on sexuality			11.0	5.0
Inadequate knowledge	577	49.3		
Adequate knowledge	594	50.7		
Attitude towards premarital sex			13.0	6.0
Permissive attitude	497	42.4		
Non-permissive attitude	674	50.7		

Table IV: Mediation effect of depressive symptoms, anxiety, and stress on the relationship between the factors and sexual risk behavior (N=1171)

Relationship	Direct effect	Indirect effect	Conclusion		p-value	Conclusion
			Lower bound	Upper bound		
ACEs > Depression > SRB	7.47 (p=0.012)*	-10.340	-27.904	-1.916	0.018*	Partial mediation
Religiosity > Depression > SRB	2.12 (p=0.011)*	-0.070	-0.250	-0.007	0.021*	Partial mediation
Knowledge on sexuality > Depression > SRB	-0.78 (p=0.136)	0.697	-0.351	4.341	0.155	No mediation
Attitude towards premarital sex > Depression > SRB	-1.22 (p=0.197)	0.033	-0.038	0.188	0.274	No mediation
ACEs > Anxiety > SRB	7.47 (p=0.012)*	-11.544	-35.743	-1.783	0.020*	Partial mediation
Religiosity > Anxiety > SRB	2.12 (p=0.011)*	-0.089	-0.363	-0.010	0.017*	Partial mediation
Knowledge on sexuality > Anxiety > SRB	-0.78 (p=0.136)	1.051	-0.142	6.510	0.085	No mediation
Attitude towards premarital sex > Anxiety > SRB	-1.22 (p=0.197)	0.034	-0.050	0.231	0.307	No mediation
ACEs > Stress > SRB	7.47 (p=0.012)*	-38.934	-128.152	-10.101	0.003*	Partial mediation
Religiosity > Stress > SRB	2.12 (p=0.011)*	-0.289	-1.254	-0.049	0.007*	Partial mediation
Knowledge on sexuality > Stress > SRB	-0.78 (p=0.136)	2.800	-0.970	19.220	0.135	No mediation
Attitude towards premarital sex > Stress > SRB	-1.22 (p=0.197)	0.189	-0.057	1.028	0.121	No mediation

Figure I below depicts the structural model for this study. The structural model has successfully fulfilled all the requirements for goodness-of-fit indices, with $\chi^2/df = 3.611$, RMSEA = 0.047, CFI = 0.943, and TLI = 0.935. The results demonstrated that MHS partially mediates the relationship between ACEs, and religiosity, and SRB. Specifically, there was a significant indirect effect of ACEs on SRB through depressive symptoms (b= -10.340, t=-1.661 p=0.018), anxiety symptoms (b= -11.544, t=-1.408, p=0.020), and stress symptoms (b= -38.934, t=-1.390, p=0.003). The same result was also observed between religiosity on SRB where there was a significant indirect effect through depressive symptoms (b=

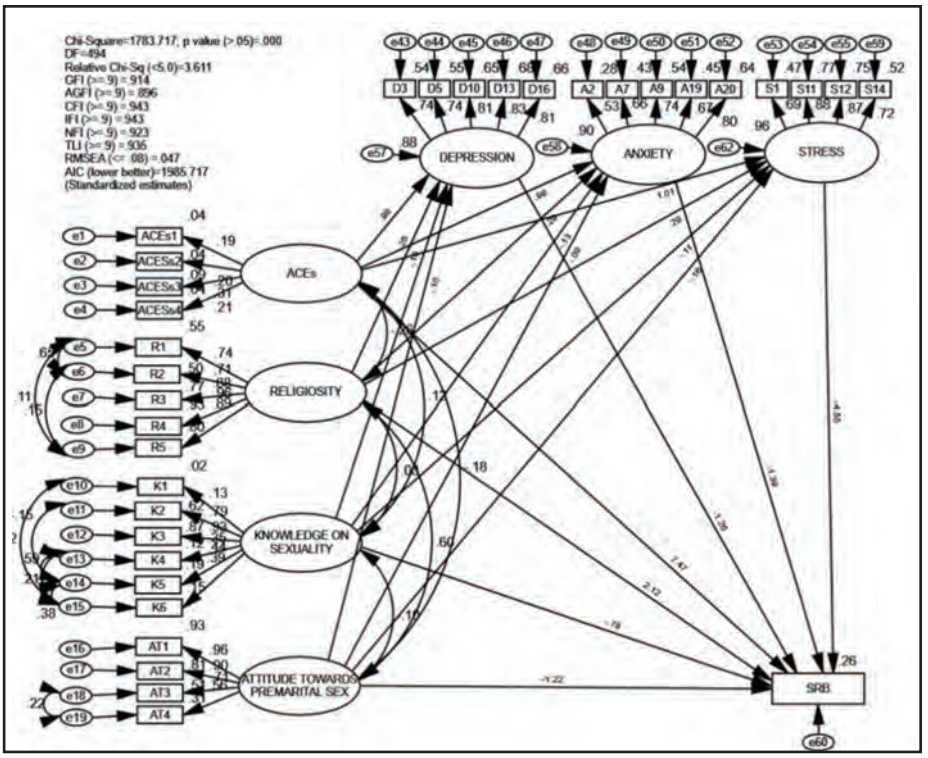

Fig. 1: Structural model of the relationship between the factors and sexual risk behaviour through depressive symptoms, anxiety, and stress (N=1171)

-0.070, t=-1.273 p=0.021), anxiety symptoms (b= -.089, t=-1.141, p=0.017), and stress symptoms (b= -0.289, t=-1.165, p=0.007). There was no mediation found for the other variables. Table IV summarise the results of the mediation effect of MHS on the studied variables.

DISCUSSION

The present study aimed to examine the mediating effect of MHS on the relationship between ACEs, religiosity, knowledge on sexuality, and attitudes toward premarital sex on SRB. The bootstrapping analysis method was used to estimate the indirect effects and the confidence intervals of the studied variables. This study demonstrates a good model fit, confirming the hypothesis. The results reveal significant indirect effects of ACEs on SRB through depressive, anxiety, and stress symptoms, as well as religiosity on SRB through depressive, anxiety, and stress symptoms. The model explains 26% of the SRB variance.

This study demonstrates statistically significant relationships between ACEs and SRB, as well as between religiosity and SRB. Specifically, individuals exposed to multiple adversities during childhood period were found to be more likely to engage in SRB9 due to the accumulation of toxic stress, which hinders the emotional development and leads to maladaptive coping strategies resulting in risky behaviours.[9,22] Additionally, religiosity plays a crucial role in the engagement in SRB due to individuals' strong personal values guided by the religion.[23,24] The statistically significant relationship between the mediators and SRB is supported by other studies.[8,13,25] It is argued that imbalanced emotions could result in poor judgement, leading to engagement in risky behaviour as a maladaptive coping mechanism.[8,25]

The prevalence of MHS among the Malaysian young adults in Malaysian tertiary education institutions have been on the rise. Anxiety remains the most prevalent at 60.5%, followed by depressive symptoms at 45.4%, and stress at 31.5%. In comparison, a previous study conducted in 2019 reported lower percentages of anxiety, depressive, and stress symptoms at 53.9%, 31.1%, and 26%, respectively.[6] A later study conducted in 2023 recorded even higher rates at 66.3%, 53.9%, and 44.6%.[14] This trend could be attributed to increased urbanisation and the consequent higher levels of perceived stress by the young adults.

Comparing to previously reported rates of SRB in a nationwide study by the National Health and Morbidity Survey (NHMS) in 2017, there has been a slight decrease in trend.[4] This study reported that 7.2% of respondents engaging in SRB, while it spiked to 7.6% in 2022.[5] This could be attributed to liberalisation and modernisation, which is largely influenced by the western cultures.[26] Nonetheless, SRB prevalence in Malaysia is relatively low compared to other Southeast Asian countries. This discrepancy may be attributed to religious and cultural factors, which contribute to Malaysia's conservative societal norms.[27]

Emotional abuse ranks the highest frequency among the type of ACEs, a finding consistent with prior studies among domestically and internationally college students.[28,29] This suggests that childhood emotional abuse is a universal trauma experienced by a significant proportion of young

adults during their childhood.[30] Apart from that, a majority of respondents report relatively high engagement in religiosity. Similarly, it was suggested that high levels of engagement and consistent participation in religious activity promotes abstinence from risky behavior.[23] This observation aligns with PBT theory, which proposes that religiosity, as a part of the personality system, can influence individuals' behaviour.[15] This could be attributed to non-organized religious activity or private religious activity being more driven by personal willingness than external influence. Religiosity traditional practices are deemed to be highly practised by those from Asian countries like Malaysia. It was also reported that Africa, the Middle East, South Asia and Latin America, are still practising the traditional forms of religiosity compared to European countries.[31]

With regard to knowledge of sexuality, a notable percentage (50.7%) of students reported adequate knowledge on sexuality, contrasting with previous studies.[32–34] Similarly, a study conducted in southern region of Malaysia, reported poor levels of knowledge on sexuality among young adults.[35] Such disparities may be attributed to variances in sample selection, with the present study focusing on tertiary education institutions, while the latter encompassed youths from the general population. It was also revealed that nearly half of the respondents reported holding a permissive stance toward premarital sexual behaviour, which is comparable to prior local findings.[36] However, the prevalence is notably lower compared to the rates observed in other Asian countries like China, Taiwan, and, Nepal.[37,38] This could be largely attributed to cultural factors, given Malaysia's predominantly Muslim population, which traditionally restricts the act of premarital sex.[39,40]

This study is a nationwide study, incorporating data collected from all regions in Malaysia. Employing probability stratified random sampling to select institutions reduces bias, and enhance the study's generalizability to the intended population.

Due to COVID-19 restrictions, data collection was conducted online, limiting the ability to employ systematic sampling at the student level. Moreover, reliance on self-reported online questionnaire increases concerns regarding social desirability bias. It is recommended that future research adopts a longitudinal study design to establish causality and explore the dynamics over time. Additionally, qualitative studies are advised to gain deeper insights into individual experiences related to variables under study.

Based on the findings from this study, it is observed that mental health is the mediator between childhood abuse and religiosity towards SRB among university students. Therefore, it is recommended that enhancement of mental health screening should be done at earlier age group. Early psychological intervention can be provided to prevent this generation from engaging in sexual risk behaviour.

CONCLUSION

This study contributes to our understanding of the underlying mechanism of SRB through mediation analysis of MHS. The findings highlight the interplay of MHS between ACEs on SRB, as well as between religiosity and SRB. No significant mediation effect was found for the other variables. Thus, this study underscores the significance of MHS in understanding SRB, particularly in addressing SRB issues among young adults in Malaysia.

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Relationship between statin use and depression among diabetic patients in Seremban: a cross-sectional study

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ABSTRACT

Introduction: Statins are one of the most commonly used drugs in primary care. Both hyperlipidaemia and diabetes have independently shown statistically significant association with depression. Conversely, patients with depression have also been shown to have increased comorbidity with and poorer control of both diabetes and hyperlipidaemia.

Materials and Methods: A retrospective cross-sectional study was conducted for about 7 months (from 23 January 2024 to 9 August 2024) among adult Type 2 diabetic patients in the non-communicable disease section of Seremban Health Clinic to determine the association between statin use and depression. The data was collected via interviewer-guided questionnaire that consisted of 5 sections: Section A (Participant Information), Section B (Depression, Anxiety and Stress Scale 21 [DASS-21]), Section C (Beliefs about Medicines Questionnaire [BMQ]), Section D (Malaysia Medication Adherence Assessment Tool [MyMAAT]) and Section E (Patient Health Questionnaire-9 [PHQ-9]). Consecutive patients that met inclusion and exclusion criteria who consent to be involved in the study were sampled. Although the ideal sample size that was required is 242, only 82 participants were enrolled in this study. These participants were also part of the Seremban Diabetes cohort study.

Results: Since only 82 participants consented to be part of this study, the response rate was 33.9%. About 25% of patients had depression. As the statin dosage intensity increased, the prevalence of depression also increased but this was not statistically significant. Based on Pearson's chi square test, only stress (p<0.001), anxiety (p=0.002), beliefs about medicines (p=0.010) and marital status (p=0.039) had a statistically significant association with depression. Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress (OR 14.000, 95% CI 2.682 - 73.076, p=0.002) was statistically significant.

Conclusion: The association between depression and statin use among patients with Type 2 diabetes mellitus is not statistically significant. Further studies are needed to confirm the cause of depression in this group of patients.

KEYWORDS:
Cross-sectional studies, Diabetes mellitus, Depression, Hydroxymethylglutaryl-CoA reductase inhibitors, Sociodemographic factors

INTRODUCTION

Statins are one of the most common medications in primary care.[1] In 2018, about 145.8 million people worldwide are taking statins.[2] In Malaysia, statins are used for primary prevention of cardiovascular diseases among high-risk individuals as well as for secondary prevention of cardiovascular diseases.[3] Despite its benefits, some studies have associated statin use with depression.[4-7] For example, a prospective cohort study in the Swedish population revealed that simvastatin was associated with reduced risk of depression while atorvastatin was associated with increased risk of depression.[4] However, there is less research regarding this association in the Malaysian population. This data could be clinically important because it can help clinicians to decide if further interventions are needed to screen for depression in the Malaysian population who are on statins.

Thus, since there is a high prevalence of cardiovascular diseases, depression and Type 2 diabetes mellitus among the Malaysian population along with less research regarding the association between statin use and depression in Malaysia.[8-10] This study was conducted to verify the association between statin use and depression among diabetic patients in Seremban, Malaysia. The other objectives of this research were to: 1) determine the prevalence of depression among diabetic patients taking statins and 2) identify sociodemographic factors that could be contributing to depression among diabetic patients.

MATERIALS AND METHODS

The inclusion criteria for study participants were adult patients aged at least 18 years at time of interview who were diagnosed with Type 2 diabetes mellitus and are taking statin therapy. On the other hand, the exclusion criteria were: 1) Patients with limited ability to understand Malay or English, 2) Patients aged 65 and above at the time of interview and 3) Patients with Type 1 diabetes mellitus. The study design was retrospective cross-sectional as patients were not followed up after they were sampled to observe for possible changes.

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This study was conducted for about 7 months (from 23 January 2024 to 9 August 2024) at the non-communicable disease section of Seremban Health Clinic, Negeri Sembilan. During the clinic's operating hours, data collection was done by members of the research team based on their availability. The method used was interviewer-guided questionnaire where a member of the research team sits with the patient as they answer the questionnaire to help provide clarification if the patient is unsure of any part of that questionnaire. This questionnaire was bilingual (Malay and English) and it consisted of five parts which were Section A (Participant Information), Section B (Depression, Anxiety and Stress Scale 21 [DASS-21]), Section C (Beliefs about Medicines Questionnaire [BMQ]), Section D (Malaysia Medication Adherence Assessment Tool [MyMAAT]) and Section E (Patient Health Questionnaire-9 [PHQ-9]). Section A was for collection of sociodemographic data on the patients (e.g. age, gender, financial status, highest education level). Section B to E were included with written permission from the authors via email.[11-14] Therefore, this questionnaire was designed to facilitate collection of necessary data related to the study's three objectives which were mentioned in the introduction paragraph.

The questionnaire was pilot tested at the study site on 7 July 2023. During this test, seven patients were interviewed: five out of seven met the inclusion criteria, the other two did not meet the inclusion criteria and none met the exclusion criteria. This test prompted revision of the questionnaire to allow for more straightforward answers by the study participants for some questions (e.g. financial status was revised to T20, M40 and B40).

Depression was assessed using DASS-21. For the reliability of the Malay version of DASS-21, a study revealed that this version had a good Cronbach's alpha value of 0.75, 0.74 and 0.79 for depression, anxiety and stress respectively.[11] On the other hand, for validity, the same study also revealed that all questions in the Malay version of DASS-21 had factor loading of more than 0.3 which is good except for 4 questions which are: D21 (0.18), A15 (0.21), A20 (0.11) and S18 (0.04).[11] The score on DASS-21 was multiplied by 2 to calculate the final score for each category. The score ranges of depression in DASS-21 was as follows: Normal (0 to 9), Mild (10 to 13), Moderate (14 to 20), Severe (21 to 27) and Extremely Severe (28 to 42). Patients who scored at least 10 in DASS-21 would be further assessed using PHQ-9. The Malay version of PHQ-9 had good internal reliability among adult female patients in a primary care clinic with Cronbach's alpha value of 0.70.[12] For Malaysia Medication Adherence Assessment Tool, the internal reliability among Type 2 diabetic patients in Malaysia was good with Cronbach's alpha value of 0.910.[13] For Beliefs on Medicine Questionnaire, the internal reliability among Type 2 diabetes patients in primary care clinics in Malaysia was good with Cronbach's alpha value of 0.74 to 0.75.[14]

Consecutive patients that met inclusion and exclusion criteria who consent to be involved in the study were sampled. Sample size, n was calculated using the following formula: $n = [z^2 \times p (1-p)] / e^2$ where z was z score, p was population proportion and e was margin of error. Our study was using a confidence level of 95% and margin of error of 5%. Thus, the z score was 1.96. Based on data from a systematic review and meta-analysis on the prevalence of depression among Type 2 diabetic patients in Malaysia, this study found that the overall pooled prevalence was 17%.[15] One of the papers cited in this study also covered Negeri Sembilan via DASS-21 questionnaire and the prevalence in that study was 16.25% which was close to the overall pooled prevalence.[15] Therefore, p in our study was set at 17%. After taking these values into consideration, the proposed sample size was 217. However, after assuming a non-response rate of 10%, the final sample size was 242.

Ethical approval from the Medical Research & Ethics Committee (MREC) was needed prior to the start of any study related activities at the study site. MREC approval was necessary to ensure that this research will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Before applying for MREC approval via the National Medical Research Register (NMRR), this research received the necessary internal, ethical approval first from the IMU University Joint Committee on Research and Ethics (IMU-JC) on 2 October 2023 with reference number of 4.6/JCM-274/2023 Bachelor of Medicine & Bachelor of Surgery (MBBS). Once IMU-JC approved this study, MREC approval was obtained via the NMRR system (dated 21 December 2023 with reference number 23-03149-QPX). After MREC approval, this study also received permission from the study site's District Health Officer which was dated as 12 January 2024 with reference number of PKS.51/671 Jld.5 (6). There was minimal involvement of potentially vulnerable subjects in this study. Children aged below 18 were excluded as they were below minimum age of consent in Malaysia. Adults aged 65 and above were also excluded as they might have cognitive impairment. Since pregnant and lactating women were not recommended to take statins due to treatment guidelines, this population might not be in our study sample. If subjects were critically ill, they were allowed to go for needed treatment first. Prisoners were also excluded from this study. On the other hand, if a patient's score indicated poorer than normal adherence to statins or higher than normal depression, anxiety or stress, the relevant person-in-charge at the Seremban Health Clinic (e.g. medical officer) would be notified to discuss if further action needed to be taken (e.g. referring patient for further assessment).

After reading and understanding the given patient information sheet and informed consent form, all participants provided verbal and written informed consent before participating in this research. If patients insisted on consulting their family members first, they were allowed to take a copy of the information sheet home. Then, if the patient was interested to join this study, the patient could contact the investigators from details given in the patient information sheet to arrange an appointment at the study site.

Dependent variable

The primary outcome for this study was depression, measured using the DASS-21. Participants were classified as having depression if their DASS-21 depression subscale score was greater than 9.

Independent variable

The primary independent variable in this study was the intensity of statin use, which was categorised based on both the type and dosage of the statin prescribed. Statin intensity was classified into three levels: low intensity, which included simvastatin 10 mg ON; moderate intensity, which encompassed simvastatin 20-40 mg ON and atorvastatin 10-20 mg ON; and high intensity, which included atorvastatin 40-80 mg ON. This categorization was based on the 2018 American Heart Association guideline on Management of Blood Cholesterol. Lipid control was assessed with LDL level using a cut-off value of 2.6mmol/L. Diabetes control was evaluated using latest HbA1c levels, with the following categories: HbA1c less than 6.5% was classified as good control, HbA1c between 6.5% and 7.9% as fairly good control, and HbA1c greater than 8% as poor control. Anxiety and stress were diagnosed using the DASS-21. For anxiety, a score greater than 7 was used to classify participants as having anxiety. For stress, a score greater than 14 was used to classify participants as experiencing stress. Beliefs about medicines were evaluated using the Beliefs on Medicine Questionnaire. Participants were categorised into four groups based on their responses: Accepting (specific necessity score ≥15, specific concerns score <15); Ambivalent (specific necessity score ≥15, specific concerns score ≥15); Sceptical (specific necessity score <15, specific concerns score ≥15); and Indifferent (specific necessity score <15, specific concerns score <15). Adherence to medication was assessed using the Malaysia Medication Adherence Assessment Tool questionnaire. Participants' adherence levels were categorised based on their scores from the questionnaire, with a score of 54 or higher indicating good adherence, and anything below indicating poor adherence.

Statistical analysis

The data was anonymously keyed into a Microsoft Excel sheet before being transferred to the Statistical Package for the Social Sciences (SPSS) software for further analysis. Data analysis was conducted using SPSS version 30.0. Descriptive statistics were used to summarise the demographic and clinical characteristics (e.g. age, financial status, marital status etc.) of the study sample. Frequencies, percentages, means, and range were calculated as appropriate. Then, frequency was used to describe prevalence of depression among patients with Type 2 diabetes mellitus who are taking statins. The frequency observed via DASS-21 and PHQ-9 was also compared to determine validity of DASS-21, as PHQ-9 incorporates the DSM-IV diagnostic criteria of depression. On the other hand, Pearson's chi-square test was used to compare the association between statin use and depression based on the intensity of statin dosage. Lastly, for sociodemographic factors that could be contributing to depression, Pearson's chi-square test was also used to identify variables that had a statistically significant association with depression. Statistical significance was set at $p<0.05$. To further refine the analysis and account for potential confounding factors, an adjusted logistic regression model was conducted. This model included all significant variables from the chi square test to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs). This approach controlled for the influence of other variables, providing a clearer picture of each variable's independent effect on depression.

RESULTS

Response rate and subject recruitment

Of the 242 people who were approached, only 82 of them consented, giving a response rate of 33.9%. The response rate was low because of two factors: 1) patients met the exclusion criteria (e.g. age of 65 and above) and 2) patients were not keen to participate in this study.

Socio-demographic characteristics of the respondents

The demographic and clinical data of all participants were shown in Table I. A total of 82 patients were recruited for this study. The predominant categories by type were: females (gender), Indians (ethnicity), married (marital status), B40 (financial background), secondary school (highest education level) and 3 or more comorbidities (number of long-term illnesses). Most participants were on at least 3 or more medications and about 75% of participants were also taking antihypertensives. More than 50% of participants were on atorvastatin and the statin dosage was mostly of moderate intensity. On the other hand, regarding diabetes control, about 66% of participants had good or fairly good control while 34% had poor control. Only 25% of participants were on insulin therapy. Most participants also had no family history of depression and never smoked or drank alcohol. The mean age was 55 years and the age range was from 36 years to 64 years.

More than 50% of participants had a poorly controlled lipid profile. However, 54% had good adherence to their medication but only 11% had an 'accepting' belief about medicines. Anxiety was present in 33 out of 82 participants (11 had mild anxiety, 9 had moderate anxiety, 4 had severe anxiety and 9 had extremely severe anxiety). Stress was present in 25% of participants (10 had mild stress, 6 had moderate stress, 2 had severe stress and 3 had extremely severe stress).

Prevalence of depression among Type 2 diabetic patients taking statins

According to PHQ-9 results, 20 patients had depression among the 82 subjects recruited (24.4%). In contrast, DASS-21 results showed 22 patients (26.8%) had depression. The minimal discrepancy in frequency (2.4%) showed that the results of PHQ-9 and DASS-21 were aligned to each other. The number of patients with depression, anxiety and stress is shown in Table II.

In Table III, validity of DASS-21 was shown by comparing its depression and non-depression rate with those of PHQ-9. It was shown that DASS-21 was highly specific (specificity 89%), and moderately sensitive (sensitivity 75%) as a tool in assessing depression. The accuracy was able to reach 85% and the positive and negative predictive values were 68% and 92% respectively. Therefore, DASS-21 was considered as a good tool for determining depression among the subjects in this study. It also provided a view of the correlation between depression and anxiety as well as stress.

Association between statin use and depression among Type 2 diabetic patients

There was an increasing trend for prevalence of depression with increasing dosage intensity. For example, the prevalence of depression was 21.4% in the low-intensity group, 24.4% in the moderate intensity group and 34.8% in the high intensity

Table I: Demographic and clinical data

		Number	Percentage (%)	Mean	Range
Gender	Male	27	32.9		
	Female	55	67.1		
Age				55	36-64
Ethnicity	Malay	21	25.6		
	Chinese	18	22.0		
	Indian	41	50.0		
	Others	2	2.4		
Marital status	Married	73	89.0		
	Divorced	2	2.4		
	Widowed	2	2.4		
	Unmarried	5	6.2		
Financial background	B40	65	79.3		
	M40	16	19.5		
	T20	1	1.2		
Highest educational level	No formal education	4	4.8		
	Primary school	10	12.2		
	Secondary school	55	67.1		
	University	13	15.9		
Occupational status	Unemployed	32	39.0		
	Working	32	39.0		
	Retired	18	22.0		
Number of long term illnesses	1	1	1.2		
	2	19	23.2		
	≥3	62	75.6		
Number of medications	<3	9	11.0		
	>3	73	89.0		
On antihypertensive	No	21	25.6		
	Yes	61	74.4		
Beta blocker	No	62	75.6		
	Yes	20	24.4		
Diuretics	No	73	89.0		
	Yes	9	11.0		
Types of statin	Simvastatin	38	46.3		
	Atorvastatin	44	53.7		
Intensity of statin	Low	14	17.1		
	Moderate	45	54.9		
	High	23	28.0		
Family history of depression	No	64	78.0		
	Yes	18	22.0		
Smoking	No	73	89.0		
	Yes	9	11.0		
Drinking alcohol	No	77	93.9		
	Yes	5	6.1		
Lipid control	Poorly controlled	42	51.2		
	Well controlled	40	48.8		
Insulin	No	61	74.4		
	Yes	21	25.6		
Diabetes control	Poor	28	34.2		
	Fairly good	33	40.2		
	Good	21	25.6		
Depression (DASS-21)	No	60	73.2		
	Yes	22	26.8		
Severity of depression (DASS-21)	Normal	60	73.2		
	Mild	10	12.2		
	Moderate	8	9.8		
	Severe	1	1.1		
	Extremely severe	3	3.7		
Anxiety	No	49	59.8		
	Yes	33	40.2		
Severity of anxiety	Normal	49	59.8		
	Mild	11	13.4		
	Moderate	9	11.0		
	Severe	4	4.8		
	Extremely severe	9	11.0		
Stress	No	61	74.4		
	Yes	21	25.6		

		Number	Percentage (%)	Mean	Range
Severity of stress	Normal	61	74.4		
	Mild	10	12.2		
	Moderate	6	7.3		
	Severe	2	2.4		
	Extremely severe	3	3.7		
Beliefs about medicines (BMQ)	Accepting	9	11.0		
	Ambivalent	27	32.9		
	Sceptical	30	36.6		
	Indifferent	16	19.5		
Adherence to medication (MyMAAT)	Poor adherence	37	45.1		
	Good adherence	45	54.9		
Depression (PHQ-9)	No	62	75.6		
	Yes	20	24.4		

More than 50% of participants were on atorvastatin and the statin dosage was mostly of moderate intensity. On the other hand, regarding diabetes control, about 66% of participants had good or fairly good control while 34% had poor control. Only 25% of participants were on insulin therapy. Most participants also had no family history of depression and never smoked or drank alcohol.

Table II: Number of patients with depression, anxiety and stress based on PHQ-9 and DASS-21

	Number	Frequency
Depression (PHQ-9)	20	24.4%
Depression (DASS-21)	22	26.8%
Anxiety	33	40.2%
Stress	21	25.6%

The minimal discrepancy in frequency (2.4%) showed that the results of PHQ-9 and DASS-21 were aligned to each other.

Table III: Validity of DASS-21

	Depression (PHQ-9)	Not depressed (PHQ-9)	
Depression (DASS-21)	15	7	22
Not depressed (DASS-21)	5	55	60
	20	62	82

DASS-21 was highly specific (specificity 89%), and moderately sensitive (sensitivity 75%) as a tool in assessing depression.

Table IV: Correlation analysis of multiple varibales with depression (DASS-21)

	Pearson chi square	P value
Gender	0.435	0.509
Ethnicity	4.149	0.246
Marital status	4.25	0.039
Financial background	0.541	0.763
Highest educational level	0.214	0.975
Occupational status	1.930	0.381
Number of long-term illnesses	1.556	0.459
Beta-blocker	1.885	0.170
Diuretics	0.109	0.741
Family history of depression	0.497	0.481
Smoking	1.598	0.206
Alcohol	0.127	0.722
Lipid control	0.018	0.894
Insulin	0.044	0.835
Diabetes control	4.053	0.132
Anxiety	9.759	0.002
Stress	22.821	<0.001
Beliefs about medicines (BMQ)	11.305	0.010
Adherence to medication (MyMAAT)	2.369	0.124

Based on Pearson's chi square test, the only sociodemographic factors that had a statistically significant association with depression were stress (χ^2=22.821; p < 0.001), anxiety (χ^2=9.759; p = 0.002), beliefs about medicines (χ^2: 11.305; p = 0.010) and marital status (χ^2=4.25; p = 0.039).

Table V: Adjusted Logistic Regression Analysis of depression and its association with marital status, stress, anxiety and belief about medicines

		Adjusted OR	p-value	95% Confidence interval
Marital status		6.178	0.050	0.998 - 38.259
Stress		14.000	0.002	2.682 - 73.076
Anxiety		1.113	0.892	0.237 - 5.224
Belief about medicines	Indifferent	ref	ref	ref
	Sceptical	0.480	0.360	0.100 - 2.312
	Ambivalent	0.295	0.145	0.057 - 1.524
	Accepting	0.000	0.999	0.000

* OR=Odd ratio
Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress was statistically significant. Beliefs about medicines were not showing statistically significant results due to its low variability of data.

group. However, this result was not statistically significant (p=0.583).

Sociodemographic factors contributing to depression among Type 2 diabetic patients

Based on Pearson's chi square test, the only sociodemographic factors that had a statistically significant association with depression were stress (χ^2=22.821; p < 0.001), anxiety (χ^2=9.759; p=0.002), beliefs about medicines (χ^2: 11.305; p=0.010) and marital status (χ^2=4.25; p=0.039). The findings from other sociodemographic factors were summarised in Table IV.

Therefore, the four statistically significant factors above were analysed further. The odds ratio of stress was 13.25 (95% CI 4.1 - 42.82), beliefs about medicines was 0.461 (95% CI 0.218 - 0.976), and anxiety was 5.00 (95% CI 1.744 - 14.34). For marital status, the odds ratio was 4.118 (95% CI 0.993 - 17.076), and its confidence interval included 1. Hence, this indicated that the result was not statistically significant. Upon adjusted logistic regression of the 4 factors (marital status, stress, anxiety and belief about medicines), only stress was statistically significant. Anxiety and marital status were not statistically significant as the 95% confidence interval of odds ratios included 1. Beliefs about medicines were not showing statistically significant results due to its low variability of data. The adjusted logistic regression was shown in Table V.

DISCUSSION

Based on the study's objective, this study had three major findings. Firstly, about 25% of the study population had depression. While this finding was higher than the overall prevalence of depression among patients with Type 2 diabetes mellitus in Malaysia, it was still within the normal range if locality-based prevalence was used.[15] This was because the prevalence ranged from 4.3% in Hulu Selangor to 36.8% in Perak.[15] This was an important negative finding as an increased rate of depression among patients with Type 2 diabetes mellitus in Malaysia would warrant further studies to determine the need for early mental health intervention in these patients.

The second major finding was the lack of a statistically significant association between statin use and depression. While this was different from other studies that have associated statin use with reduced risk of depression, it was important to note that a study in Denmark explained that the association could be due to residual confounding bias such as coming for more follow-up visits due to statin therapy.[7] This was another significant negative finding as it would not make clinicians hesitate to prescribe statins for patients with depression when there was a clinical indication such as prevention and treatment of cardiovascular diseases.

The third major finding was the presence of one sociodemographic factor (stress) that had a statistically significant association with depression. The association with stress and increased risk for depression was also similar to what was reported in other studies. For example, in a study in Germany, 3 domains of chronic stress (Pressure to Perform, Social Isolation and Chronic Worrying) had a statistically significant association for increased risk of depression.[16] These sociodemographic factors are important positive findings as they might represent modifiable risk factors that could be tackled via effective health policies.

Although cholesterol had important normal functions in the central nervous system, this was an important contribution to cardiovascular disease prevention because high cholesterol levels were a risk factor for cardiovascular diseases especially in diabetic patients.[17-18] Statins helped to reduce cholesterol levels by competitively inhibiting the rate-limiting enzyme of the cholesterol synthesis pathway which is HMG-CoA reductase.[19] While statin use did not have a statistically significant association with depression among this study's participants, other studies had reported that the use of statins was associated with a reduction in risk of depression in people under the age of 40 years.[4]

Lipid control was also not shown to have a statistically significant association with depression in this study. However, other studies have reported otherwise. For example, hyperlipidaemia was linked with increased rates of depression.[20] This tied in with the fact that both hyperlipidaemia and diabetes had independently shown statistically significant association with depression.[21] Conversely, patients with depression had also been shown to have increased comorbidity with and poorer control of both diabetes and hyperlipidaemia.[22]

It was also important to note that all of the participants in this study were also part of the Seremban Diabetes (SeDia) cohort study and this could affect the study results. SeDia cohort study was officially launched by Duli Yang Maha Mulia Yang Di Pertuan Besar Negeri Sembilan, Tuanku Muhriz ibni Almarhum Tuanku Munawir on 10 July 2023.[23]

This initiative involved the Ministry of Health of Malaysia and IMU University.[23] SeDia cohort study was the first large-scale cohort study on diabetes in Malaysia as it involved a 12-year longitudinal open observational cohort study of previously diagnosed and newly diagnosed diabetes patients, who registered with the National Diabetes Registry at Seremban Health Clinic, along with their household family members.[24] An example of a factor which could be affected was medication adherence. For example, participants would have been counselled about this matter leading to better lipid control and diabetes control. This could lead to lack of statistically significant findings in regards to medication adherence.

On the other hand, this study had some limitations. Firstly, the target sample size of 242 patients for an ideal data analysis was not achieved. This might affect the internal validity of the study due to possible selection bias. Secondly, this study only involved 1 location. Hence, the results might not give an accurate general view of the association between statin use and depression among all patients with Type 2 diabetes mellitus. Thirdly, duration of statin therapy, duration of diabetes, complications of diabetes, quality of sleep and presence of cognitive impairment were not obtained and these could be confounders in the association between statin and depression among patients with diabetes mellitus. Fourthly, while our study could pick up possible undiagnosed cases of depression, we were unable to determine if the depression was due to statin use. This was because a retrospective study was done instead of a prospective study. Fifthly, this study did not involve any hydrophilic statins. Thus, a comparison could not be made between the association of depression with hydrophilic statin use or lipophilic statin use. This is important as other research had found that lipophilic statins (e.g. simvastatin) not hydrophobic statins were associated with a statistically significant reduction in risk of depression.[4]

The recommendations for further research are as follows: 1) conduct follow-up for patients that were involved in this study to identify possible causal links between statin use and depression, 2) carry out similar research but in areas with different population demographics (e.g. race, socioeconomic status, country) to verify if the observations are similar to what was seen in this study and 3) include hydrophilic and lipophilic statins in the study to determine if there is any difference in their association with depression.

CONCLUSION

This study showed that the association between depression and statin use among patients with Type 2 diabetes mellitus was not statistically significant. Hence, the null hypothesis was accepted. However, further studies are needed to confirm if the depression that was seen in this group of patients was due to statin use. Most importantly, patients with long-term illnesses should be compliant to the medical and lifestyle interventions for their respective conditions. Through good control of these long-term illnesses, the psychiatric morbidity can be reduced.

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Knowledge and attitude of basic cardiopulmonary resuscitation among home-based child daycare caregivers in Kelantan

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ABSTRACT

Introduction: Cardiopulmonary resuscitation (CPR) is indeed a basic skill that should be acquired by everyone in the community. Early CPR is an important element in the chain of survival and home-based child daycare (HBCD) caregivers play a vital role as early responders in case of out-of-hospital cardiac arrest (OHCA). The study aims to determine the level of knowledge and attitude of CPR among HBCD caregivers in Kelantan and the factors that contribute to them. This study covers a research gap in Kelantan, Malaysia, evaluating HBCD caregivers' knowledge and attitudes towards CPR.

Materials and Methods: This was a quantitative cross-sectional study conducted from November 2020 until March 2021 which involves 139 HBCD caregivers in Kelantan. Validated questionnaire was used which consisted of 27 questions based on demography, knowledge and attitude towards CPR. The data was keyed in and analysed using software SPSS version 26.

Results: A total of 139 respondents participated in the study. The mean attitude score obtained by the caregivers was 16.67 with SD = 4.22. There were 89 caregivers (64%) with poor knowledge among the 139 HBCD caregivers in the study compared to 50 HBCD caregivers (36%) who had good knowledge. Caregivers who were exposed with CPR training had 5.91 higher odds of having good CPR knowledge compared to those without being exposed to CPR training (Wald-statistic (df) = 21.12 (1), OR (95% CI) = 5.91 (2.77, 12.61), p<0.001). Caregivers with experience in handling CPR were 5.91 of higher odds in having good CPR knowledge compared to those without the experience in handling CPR when adjusted for the duration of caregiver's experience (Wald-statistic (df) = 21.12 (1), OR (95% CI) = 5.91 (2.77, 12.61), p<0.001). HBCD caregivers' experience was the only variable that had a significant p-value when tested in the regression model (p = 0.023).

Conclusion: The findings revealed that HBCD caregivers in Kelantan had inadequate CPR knowledge, potentially increasing the risk of OHCA. Planned and regular training for them is mandatory. Exposure to CPR was the associated factor that contributes to knowledge level among HBCD caregivers whereas years of experience as HBCD caregivers influence attitude towards CPR.

KEYWORDS:
Knowledge, attitude, Cardiopulmonary resuscitation, HBCD caregivers, Cardiac arrest

INTRODUCTION

Cardiopulmonary resuscitation (CPR) has evolves into life-saving procedure and is no longer limited to healthcare personnel.[1] There is a theory that without CPR, a person's chances of survival drop by 7-10% per minute.[2] The Resuscitation Council of Asia had conducted large observational studies that show the positive impact of bystander CPR on survival following out-of-hospital cardiac arrest.[3]

There were more than 5000 cases of paediatric cardiac arrest out-hospital annually in the United States of America.[4] The majority of the cases were caused by respiratory causes rather than heart origin.[5] Like adults, most children who experience out-of-hospital cardiac arrest did not receive CPR from a bystander.[6]

Because of the parents' job obligations and busy schedules nowadays, child daycare caregivers are in high demand. In the last two decades, Malaysia's child daycare gross enrolment ratio had risen from 55 to 80%. Therefore, it is critical that child daycare caregivers have the necessary knowledge and expertise to deal with cardiac arrest (CA).[7] In Malaysia, parents have the options of sending their children to kindergarten, nurseries, or home-based daycare. While most kindergarten and nurseries were supervised and registered under Jabatan Kebajikan Masyarakat and / or Kementerian Pendidikan Malaysia, home-based child daycare is not obligated to do so (as they only cater for three children and below under their care). Therefore, in Kelantan state, they were regulated under Secretariat Welfare, Woman & Family Development (U-KeKWa). Despite the fact that emergencies often occur in child daycare centres, the caregivers, who were typically the first responders, frequently lack basic training skills including CPR.[8]

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Cardiac arrest in children might be a rare encounter. However, as most of the cases stemmed from respiratory issue (eg. chocking etc, especially in young child), the risk of getting CA in a daycare centre is real and should not be dismissed lightly. Since home-based child daycare (HBCD) caregivers may encounter cases of cardiac arrest at any point of time and due to the limitation of information regarding CPR among this population in Malaysia particularly Kelantan, the current study aims to assess the gap of knowledge and attitude of basic CPR among HBCD caregivers as well as the factors associated with them. It is hoped that the findings of this study can be used to design more effective and appropriate intervention strategies.

MATERIALS AND METHODS

Study design and duration

This observational, cross-sectional study was conducted between 1st November 2020 until 31st March 2021 in the state of Kelantan. The study population involved 139 caregivers who fulfilled the study criteria.

Reference population

HBCD caregivers in Kelantan, Malaysia.

Source population

HBCD caregivers in Kelantan that acquired from U-KeKWa in the state of Kelantan, Malaysia.

Sample frame

HBCD caregivers in Kelantan, Malaysia that acquired from U-KeKWa in the state of Kelantan, Malaysia who fulfil the inclusion criteria.

Sample size and sampling method

Sample size calculated was 70. Sampling method was done using non-probability sampling (convenient sampling) where all participants who fulfil the inclusion and exclusion criteria were included. There are about 200 HBCD caregivers registered with U-KeKWa office of Kelantan. They were interviewed either primarily through child daycare visit or telephone call.

Research tools

Data collection was done using a questionnaire (Malay language) from a validated survey, adapted from Rahman et al (2013) titled Knowledge and Attitude about CPR among School Children in Malaysia. The questionnaire was divided into 3 sections, namely demographic, knowledge and attitude, with total of 27 questions. Each question contributes 1 mark, making a total of 12 marks for knowledge assessment. Respondents are considered to have good knowledge if they score ≥ 8 out of 12. However, in this study participants would be considered to have good knowledge if they score ≥8 out of 10 questions under the knowledge domain which addresses their knowledge understanding specifically (Question 5-12) and not their exposure to knowledge (Question 1-4).

There are 8 questions in the attitude and perception section. Responses to the statements were "strongly agree," "agree," "not sure," "disagree" and "strongly disagree." The items were given a score of four for strongly agree, three for agree, two for not sure, one for disagree and zero for strongly disagree. A total possible maximum score in the attitude domain was 32.

As far as the validity of the questionnaire is concerned, in terms of knowledge domain on CPR, all loadings of items in this domain construct range 0.527 to 0.856. In attitude domain, factor loading for attitude ranges from 0.462 to 0.922.

Cronbach's alpha wase used to assess internal consistency of the factors. For knowledge domain on CPR, the Cronbach's alpha was 0.435 and 0.572. For attitude domain, the Cronbach's alpha was 0.651 and 0.871.

Data collection method

Eligible subjects were briefed regarding the study details for about 5 minutes and were given the written consent form. The written consent form and questionnaire were handled in Bahasa Malaysia as all eligible participants did not have good English proficiency skills. Subjects were instructed to answer the questions within 30 minutes and the questionnaire was collected after 30 minutes. Investigator checked the questionnaire for completeness.

Ethical considerations

Data privacy and protection is kept confidential only by the researcher. Consent was also taken using the consent form prepared. All ethical concerns were already being taken care of as per the ethical committee recommendation. This study received ethical boards approvals from Human Research Ethics Committee of USM (USM/JEPeM/20060325).

Statistical analysis

All statistical analyses were done using IBM Statistical Package for the Social Science (SPSS) version 26. Frequency and percentage were reported for categorical variables. For numerical variables, mean and standard deviation (SD) were reported when the observations were normally distributed. Otherwise, median and interquartile range (IQR) were reported.

For descriptive analysis, frequency and percentage of poor and good were reported for knowledge level while mean and SD were reported for attitude score.

To study the factors associated with good knowledge among HBCD caregivers, univariable analysis, the simple logistic regression, was done to screen independent variables (exposed to CPR, previous CPR training and caregivers' experience) that at least had an association with knowledge. The model goodness-of-fit was then assessed by performing Hosmer-Lemeshow test,[9] overall correctly classified percentage, and area under the Receiver operating characteristic (ROC) curve.

Simple linear regression was done to determine variables that at least had an association with attitude towards CPR. Significant p-value ($p<0.05$) indicates significant association between independent variable and attitude towards CPR. Next, independent variable with $p<0.25$ was included in

Table I: Descriptive analysis of experience and willingness to do CPR by HBCD caregivers (n = 139)

Variable	Frequency (%)
HBCD caregivers experience	
<1 year	1 (0.7)
1-5 years	63 (45.3)
5-10 years	30 (21.6)
>10 years	45 (32.4)
Number of children under their care	
<5	123 (88.5)
5 – 10	9 (6.5)
>10	7 (5.0)
Exposed to CPR	
No	84 (60.4)
Yes	55 (39.6)
Previous CPR training	
<6 months	33 (23.7)
>6-12 months	6 (4.3)
1-2 years	1 (0.7)
>2 years	14 (10.1)
Not related[a]	82 (59.0)
Missing observations	3 (2.2)
Willingness to do Mouth to mouth CPR to family member	
No	10 (7.2)
Yes	112 (80.6)
Don't know	17 (12.2)
Willingness to do Mouth to mouth CPR to outsiders	
No	43 (30.9)
Yes	14 (10.1)
Don't know	82 (59.0)
Keen to learn CPR	
Disagree	2 (1.4)
Agree	122 (87.8)
Not sure	15 (10.8)

[a] Caregivers who never exposed to CPR

Table II: Frequency of right and wrong answer in knowledge towards CPR section

Question number	Item	Frequency (%)	
		Right	Wrong
1	A is for Airway	99 (71.2)	40 (28.8)
2	B is for Breathing	78 (56.1)	61 (43.9)
3	C is for Circulation	55 (39.6)	84 (60.4)
4	Chest compression per minute	75 (54.0)	64 (46.0)
5	Ratio of chest compression	74 (53.2)	65 (46.8)
6	Quick response	85 (61.2)	54 (38.8)
7	Number of breaths	64 (46.0)	75 (54.0)
8	Location of chest compression	111 (79.9)	28 (20.1)
9	Emergency number	136 (97.8)	3 (2.2)
10	Open airway technique	110 (79.1)	29 (20.9)

Table III: Descriptive analysis of attitude score by independent variables

Variable	Frequency (n)	Attitude score, Mean (SD)
Exposed to CPR		
Yes	55	16.55 (3.91)
No	84	16.75 (4.44)
Previous CPR training[a]		
≤2 years ago	38	15.95 (3.94)
>2 years ago	14	17.00 (7.00)[b]
Caregivers experience		
<5 years	64	16.00 (8.00)[b]
≥5 years	75	16.00 (4.00)[b]

[a] Analysed among caregivers being exposed to CPR (n = 52)
[b] Median (IQR)

Table IV: Associated factors of CPR knowledge level among HBCD caregivers by simple logistic regression analysis and multiple logistic regression analysis

Variable	Knowledge level, n (%)		Regression coefficient (b)	Wald statistic (df)	Odds ratio, OR (95% CI)	p-value
	Poor (n = 89)	Good (n = 50)				
	Model: Simple logistic regression					
Exposed to CPR						
No	67 (75.3)	17 (34.0)	0	21.12 (1)	1	<0.001
Yes	22 (24.7)	33 (66.0)	1.78		5.91 (2.77, 12.61)	
Previous CPR training[a,b]						
>2 years ago	5 (23.8)	9 (29.0)	0	0.17 (1)	1	0.677
≤2 years ago	16 (76.2)	22 (71.0)	-0.27		0.76 (0.22, 2.72)	
HBCD caregivers experience[a]						
<5 years	45 (70.3)	19 (29.7)	0	2.02 (1)	1	0.155
≥5 years	44 (58.7)	31 (41.3)	0.67		1.67 (0.82, 3.38)	
Model: Multiple logistic regression[c]						
Exposed to CPR						
No	67 (75.3)	17 (34.0)	0	21.12 (1)	1	<0.001
Yes	22 (24.7)	33 (66.0)	1.78		5.91 (2.77, 12.61)	

[a] Recode into two categories
[b] Analysed among HBCD caregivers whose being exposed to CPR (n = 55, missing observation = 3 were excluded from the analysis); Poor knowledge (n = 21) and good knowledge (n = 31).
c Forward LR Multiple Logistic regression was applied.
Multicollinearity and interaction checking were not applicable.

Table V: Associated factor of Attitude towards CPR by simple linear regression and multiple linear regression analysis

Variable	Regression coefficient, b (95% CI)	t-statistic	p-value	Coefficient of determination, R2
	Model: Simple linear regression			
Exposed to CPR				
No[a]	-			
Yes	-0.21 (-1.66, 1.25)	-0.28	0.781	0.001
Previous CPR training[b]				
>2 years ago[a]	-			
≤2 years ago	-2.34 (-4.80, 0.12)	-1.91	0.062	0.068
HBCD caregivers experience				
<5 years[a]	-			
≥5 years	-1.63 (-3.03, -0.23)	-2.30	0.023	0.037
Model: Multiple linear regression[c]				
HBCD caregivers experience				
<5 years	-			
≥5 years	-1.63 (-3.03, -0.23)	-2.30	0.023	0.037

[a] Analysed among HBCD caregivers whose being exposed to CPR (n = 52)
[b] Reference group
[c] Stepwise multiple linear regression method applied. Multicollinearity and interaction checking were not applicable. Model assumptions (Normality distribution of residual, equal variances, and linearity) were fulfilled.

multiple linear regression analysis for variable selection by forward selection, backward elimination, and stepwise method. Multicollinearity and interaction checking were not applicable.

Assumptions for the linear regression model were checked.[10] Normality distribution of the residual was determined by plotting histogram and boxplot. Variances were equal when there was no divergent or convergent pattern on the scatter plot. Regression coefficient with 95% CI, t-statistic, and p-value were reported as the results of the analysis. The variable with significant p-value (p<0.05) and 95% CI of regression coefficient not across zero was considered as a significant associated factor. Coefficient of determination (R2) was also reported.

RESULTS

A total of 139 respondents participated in the study. All of them were Malay female where most of them were between 41 to 50 years old (40.3%). There were only two caregivers above 60 years old (1.4%). The education background of most of them was secondary school (n (%) = 129 (92.8)). A total of 79.1% of them were married.

As for the knowledge, among 139 HBCD caregivers in the study, there were only 50 (36%) caregivers possessed good knowledge, ie. able to score at least 8 out of 10 questions correctly.

Table II showed the frequency and percentage of participants answering the right and wrong answers for each item in knowledge section. Almost all items were correctly answered by the participants except for question number 3 and 7, where more than 50.0% of participants answered the wrong answer.

For response frequency of items in attitude and perception towards CPR among HBCD caregivers, more than 40.0% of respondents answered "Unsure" in all eight items.

The mean attitude score obtained by the caregivers was 16.67 with SD = 4.22. The minimum and maximum score were 6 and 27, respectively. Table III below showed a descriptive analysis of attitude scores by independent variables.

Table IV showed the result of simple logistic regression analysis to determine the associated factors of good CPR knowledge among HBCD caregivers. Exposed to CPR resulted in high significant odds ratio (OR) and p-value in the regression analysis. It was found that, caregivers who were exposed with CPR training were 5.91 higher odds in having good CPR knowledge compared to those without being exposed with CPR training (Wald-statistic (df) = 21.12 (1), OR (95% CI) = 5.91 (2.77, 12.61), p<0.001). However, previous CPR training resulted in insignificant p-value (p> 0.05). Same holds true with duration of experience as a caregiver (p> 0.05).

The result in Table IV for the multiple logistic regression analysis showed that there was a significant association between exposed to CPR training status and level of CPR knowledge. Caregivers with experience in handling CPR were 5.91 higher odds in having good CPR knowledge compared to those without the experience in handling CPR when adjusted for the duration of caregiver's experience (Wald-statistic (df) = 21.12 (1), OR (95% CI) = 5.91 (2.77, 12.61), p<0.001). The model could correctly classify 71.9% of cases. Area under the ROC curve was 0.71, which indicates the acceptable discrimination between cases.

Multicollinearity and interaction checking were not applicable.
P-value of Hosmer-Lemeshow test for goodness-of-fit was not generated by the software; Overall correctly classified percentage = 71.9%; Area under the ROC curve = 0.71 (p<0.001).

Table V showed the results of simple linear regression analysis. HBCD caregivers' experience was the only variable that had a significant p-value when tested in the regression model (p = 0.023). The result indicated that, caregivers with the experience of five years and above had 1.63 less score of attitudes towards CPR as compared to those with the experience of less than five years (b (95% CI) = -1.63 (-3.03, -0.23), p = 0.023).

The result in Table V for the multiple linear regression analysis showed that there was a significant linear negative relationship between duration of caregivers' experience and attitude towards CPR score. Those with above five years' experience as a caregiver had 1.63 less score in attitude as compared to those with less than five years' experience (b (95% CI) = -1.63 (-3.03, -0.23), p = 0.023). Furthermore, the coefficient of determination implies that only 3.7% of the variation in attitude score is explained by duration of caregivers' experience according to the linear regression model (R2 = 0.037).

DISCUSSION

OHCA in Malaysia had a survival rate of fewer than 1% whereas, in developed countries, life expectancy is found to be better than 25%.[11] CPR, especially bystander CPR, had been recognised as critical for surviving cardiac arrest, as many cardiac arrest events occur at home and in public locales.[12,13] The "chain of survival" which includes early access to the Emergency Medical System, early chest compression, early defibrillation, and early advanced life support has been shown to improve OHCA outcomes as advocated by American Heart Association.[14]

International studies on a bystander's willingness to do mouth-to-mouth ventilation, also known as rescue breathing on a stranger had discovered significant differences. In Australia, 47% of people would perform rescue breathing on a stranger, whereas in the United States 15%, and in Japan only 2-3%.[15-17] Comparatively, our study showed about 80% of participants were willing to do rescue breathing on their family members but only 10% were willing to do rescue breathing on a stranger. In American study, the main concern was the risk of contracting HIV, despite the fact that the risk of getting HIV by rescue breathing is extremely low.[16] On the other hand, worry of not conducting rescue breathing correctly was reported as the major barrier in the Japanese study, despite the imminent outcome of untreated apnoea.[17] The 2017 Paediatric Basic Life Support Recommendations suggested that chest compressions with rescue breathing should be provided for paediatric cardiac arrest. However, if laymen were unwilling or unable to deliver rescue breathing, they recommended that rescuers provide chest compression only.[18]

We found that in our study, exposure to CPR was found to be a factor that contributed to the knowledge level among HBCD caregivers (p<0.01) whereby 64% of participants had poor knowledge. The result came to no surprise as more than half of the participants had never been exposed to CPR. Therefore developing structured training is highly needed.[19] Increased education efforts can be aided by public awareness campaign and active participation by primary healthcare clinicians. In addition, online courses may help in gaining theoretical knowledge of CPR but might not be effective for practicing CPR skills.[20,21] Many studies had shown that teaching CPR to non-medical personnel is the ideal way to educate the public at large about this lifesaving procedure.[12,22,23]

Another aspect to consider for effective resuscitation is positive attitude. Reluctance to perform CPR was seen in nearly one-fourth of the participants, and a shift to a more positive attitude was linked to more experience, seniority, and previous training.[24] We found that years of experience as HBCD caregivers influence attitude towards CPR (p=0.023). It was mentioned that those with less experience would have a better attitude towards CPR. The possible reason behind this is that those who are new in working as HBCD caregiver are more enthusiast, energetic and ready to learn new knowledge in order to equip themselves in becoming a good HBCD caregiver. In addition, previous CPR training had a good impact on knowledge and attitude, which could also be a motivating agent.[25] Another local study from Universiti Sains Islam Malaysia showed the child care providers had moderate attitude on CPR.[26] On the other hand, our study found a majority of 40% of participants responded "unsure" in answering questions on attitude towards practicing CPR among their clients.

There were some limitations to this study. It was carried out in the Malaysian state of Kelantan, which may have limited data heterogeneity. Secondly, gender, race, education, and marital status all had remarkable differences in distribution. However, in the statistical analysis, these elements were not deemed important. Furthermore, subject reporting bias was a concern with self-administered questionnaires. It was possible that respondents won't take the time to provide an accurate and fair evaluation of their knowledge and attitudes. On the self-administered questionnaires, there were several eliminations done due to missing values or non-responses from respondents. Other than that, there was also an issue of possible language barrier since the questionnaire was written in standard Malay, instead of Kelantanese dialect. However, this risk was reduced by the presence of investigator team with the respondents during the data collection process to facilitate accordingly if needed. The respondents were also being explained on the CPR procedure to enlighten them further.

CONCLUSION

This study revealed that HBCD caregivers in Kelantan had inadequate CPR knowledge, potentially increasing the risk of OHCA. Exposure to CPR was the associated factor that contributes to knowledge level among HBCD caregivers whereas years of experience as HBCD caregivers influence attitude towards CPR. Therefore, it is important for the necessary stakeholders and relevant authorities to have a dedicated and structured training for them. CPR training must be a prerequisite for HBCD caregivers as part of their required programmes.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Training and testing of integrated professional skills in management of shoulder dystocia among Malaysian Health Care Providers

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ABSTRACT

Introduction: To evaluate if the Intensive Course in Obstetric Emergencies (ICOE) Shoulder dystocia simulation training module could improve psychomotor and cognitive skills in the management of shoulder dystocia using a Test of Integrated Professional Skills (TIPS).

Materials and Method: This was a prospective observational study involving Malaysian health care professionals participating in ICOE shoulder dystocia simulation, where standardized curriculum was used. Pre and post-test skills assessment were conducted to evaluate the effectiveness of the course content and delivery.

Results: 609 Malaysian health care professionals attended ICOE training; 400 midwives, 128 medical officers, 55 specialist and 26 consultants. Participants were derived from 25 consecutive courses, from 2014 to 2019 and tested on predetermined skills in the management of shoulder dystocia. Their mean TIPS pre-test vs post-test score were (2.55 vs 6.77) midwives, (3.78 vs 7.25) medical officers, (5.16 vs 7.82) specialists & (3.62 vs 6.88) consultants. All four group of participants showed statistically significant improvement (51-165%) in their skills (p<0.001). The mean post test score in noting time of dystocia and call for help were significantly higher among midwives than others. All four groups statistically improved their delivery skills in McRoberts manoeuvre and directed suprapubic pressure. Pre-skills for delivery of the posterior arm was suboptimal and post skills test showed statistically significant improvement in all four groups.

Conclusion: ICOE shoulder dystocia simulation training module improved the psychomotor and cognitive skills in the management of delivery of shoulder dystocia.

KEYWORDS:
Simulation training, obstetric emergency, clinical competence, Shoulder dystocia, Mc Robert's Manoeuvre, Malaysian health care professionals

INTRODUCTION

Shoulder dystocia is a well-documented obstetric emergency, that may result in significant maternal and perinatal morbidity and mortality, when managed by a poorly trained birth attendant. The birth attendants should be adequately trained and competent to reduce the occurrence of adverse events. The Simulation and Fire-drill Evaluation Study, a simulation training of health care professional improved the effectiveness of shoulder dystocia management. This was with the use of high-fidelity mannequins which used traction force monitors, and this resulted in a reduction of the mean traction force used during delivery.[1] Targeted shoulder dystocia training for all maternity staff has been shown to be associated with a reduction in neonatal injury in births complicated by shoulder dystocia.[2]

Intensive Course in Obstetric Emergencies (ICOE) is a simulation-based training program developed, conducted and funded by the Obstetrical and Gynaecological Society of Malaysia (OGSM) since 2014. It is a comprehensive skills-based course conducted over two days to cover various obstetric emergencies. This course is conducted in Malaysia and in Southeast Asian countries by certified principal trainers who require revalidation every three years. In addition to training of birth attendants, it enables them to be revalidated. OGSM developed the curriculum, training methods, testing and mannequins required for the participants and the courses conducted are not-for-profit. Details of the curriculum can be found on the handbook published by the society.[3] This course has received numerous positive feedback from participants and external quality assessors. It is also endorsed by Asia Oceania Federation of Obstetrics and Gynaecology.[4]

Obstetricians and midwives should be competent in performing various manoeuvres to aid delivery when shoulder dystocia is encountered. They must integrate a wide range of technical skills (psychomotor) and non-technical skills (Cognitive) to handle this emergency. Assessment tools to evaluate the efficacy of training to improve these professional skills are limited.[5] Hence, we developed a structured testing tool, which could be applied before and after training. This 'Testing tool the Integrated Professional Skills' (TIPS) to manage shoulder dystocia was used to assess our ICOE course participants improvement of psychomotor and cognitive skills. TIPS is a multi-station, simulation-based assessment that incorporates complex clinical scenarios, technical and non-technical skills (ex. communication skills).

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It comprises a set of assessment matrix used amongst obstetrics and gynaecology residents to evaluate Accreditation Council for Graduate Medical Education competencies. One essential component integrated into this test is the feedback from the faculty.[5] ICOE uses a modified-TIPS approach and expanded this to include a pre and post-test component. It also emphasized the importance of feedback; providing timely, individualized directed learning on gaps which were identified. The objective of this study is to demonstrate that TIPS before and after ICOE shoulder dystocia simulation training module improves the psychomotor and cognitive skills in management.

MATERIALS AND METHODS

Health care providers (HCP) staff-nurses, midwives, medical officers, specialists and consultants from Malaysia enrolled for the ICOE course were sent a welcome note informing them about the pre and post training test using TIPS. The ICOE Handbook of Obstetric Emergencies were sent electronically or provided as hard copy and given a week before as part of the course reading material.

Participants of this study were from 25 courses from 2014 till 2019 – over a 5-year period. After completion of the knowledge test, participants underwent TIPS, where each participant spent two minutes to assess the predetermined skills listed below in the management of shoulder dystocia. The skills tests were assessed by the ICOE trainers assigned before and after the course. ICOE trainers are specialist who have undergone the Intensive Course in Obstetric Emergencies followed by Training of the Trainer Course (TOT). They are credentialled and revalidated every three years to test the skills of participants.

Four essential components were tested on the management of shoulder dystocia which were basic skills required by the practicing health care professional to successfully accomplish safe delivery.[6]

1. **Note the time and call for help:** Health care professional notes the time when the incident occurs, which helps to determine the delay in head to shoulder delivery interval, this duration is an essential component that predicts perinatal morbidity. Call for help to involve other health care professionals for multidisciplinary team management (paediatrician, anaesthetist, consultant and other birth attendants) to accomplish safe childbirth.
2. **McRobert's manoeuvre:** With the help of two assistants, both knees should be flexed, hips hyperflexed, abducted and externally rotated over the maternal abdomen. This manoeuvre causes cephalad rotation of the pelvis relieving the anterior shoulder obstruction.
3. **Directed suprapubic pressure:** With both hands applying pressure just above the symphysis pubis over the fetal back towards the face to adduct and rotate the shoulders to the oblique diameter of the pelvis.
4. **Delivery of the posterior arm:** Identify (Right or Left) the posterior arm of the baby, insert the cupped (Right Hand for Right Arm / Left Hand for Left Arm) into the hollow of the sacrum. If the fetal arm is extended the participant should flex the cubital fossa and grasp the wrist and deliver the posterior arm. This manoeuvre reduces the bi-acromial diameter to a shorter axillo-acromial diameter that facilitates delivery. This manoeuvre has been recommended over other manoeuvre by the American college of Obstetricians and Gynaecologists.[7]

The test was limited to the above manoeuvres as these have a high success rate in accomplishing the delivery of the fetus. Therefore, other internal rotational manoeuvres were not tested. The Marking scheme is shown in Table I.

Manikins and equipment

Sim-Mom and baby Model (Laerdal) was used to assess the skills.

Simulation training

All participants were given a short lecture and shown a demonstration video of shoulder dystocia skills during the course. Participants were then divided into three groups of 6-8 participants per station and spent twenty-five minutes rotating between various skills station. The skills were initially demonstrated by ICOE trainers and they were given time to practice their skills consisting of the above manoeuvres in twenty-five minutes. In each station, participants are expected to acquire, adopt or refine their knowledge and technique on a predefined skill. This may occur via one of several processes including demonstration, deconstruction of manoeuvres or small group discussions moderated by a member of the faculty. Each station ends with a summary of salient points and/or frequent errors committed during an obstetric emergency. After twenty-five minutes, the participants will move on to the next station, for example on vaginal breech delivery or cord prolapse. Upon completion of the course, they were tested by the designated ICOE trainer.

Statistical analysis

Statistical Package for Social Sciences XXI was used to analyse the data, descriptive statistics and categorical data were analysed as percentages. The mean pre and post skills score were compared and p values calculated. To compare the mean scores between subgroups Wilcoxon and Kruskal Wallis test were employed due to non- normal distribution. Each category of HCPs improvement percentage was analysed using the formula, improvement score/pre skills score x 100.

RESULTS

Descriptive analysis

A total of 609 participants attended courses as shown in Table II, the HCPs were categorized into four groups as Midwives, Medical officers (doctors and residents in specialist training programme), Specialists (Obstetrician with postgraduate qualification with less than five years of working experience) and consultants, (Obstetricians with postgraduate qualification with more than 5 years' working experience). The age range in years of the ICOE participants as shown in Table III.

Comparison of the mean TIPS scores, improvement percentage and p values between pre and post shoulder dystocia skills training are shown in the Table IV.

Table I: The marking scheme

NO	ACTION	MARKS
1	**Time and call for help:**	
	- Note the time of diagnosis and call for help	1
2	**McRobert manoeuvre:**	
	- McRoberts Position: Lie flat, flex the knee and hip	1
	- Abduct and externally rotate the hips	1
3	**Directed suprapubic pressure:**	
	- Note position of fetal back / face	1
	- Proper direction and two hand technique. Continuous pressure	1
4	**Delivery of the posterior arm:**	
	- Use the correct hand (right or left) depending on the fetal shoulder	1
	- Cupping of the hand to insert into hollow of pelvis	1
	- Flexing of the elbow	1
	- Delivering of the posterior shoulder by pulling on the wrist	1

Table II: Category of health care professionals

Category HCP	n=609	%
Midwives	400	65
Medical Officers	128	21
Specialists	55	9
Consultants	26	4.2

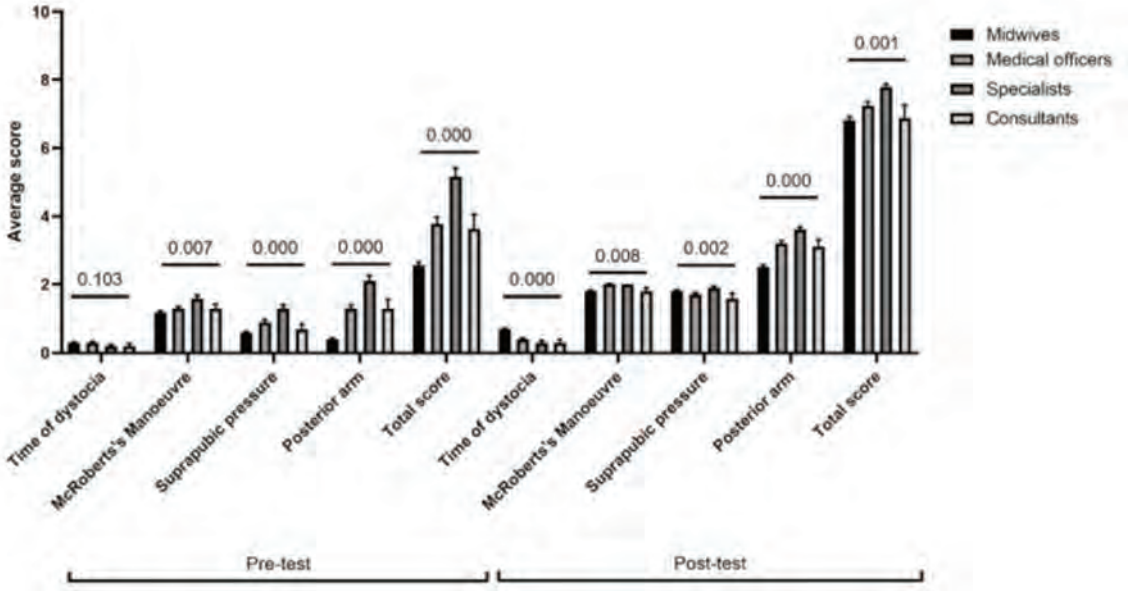
Table III: Age in years

Category HCP	n=609	Age in years
Midwives	400	23-45
Medical Officers	128	28-35
Specialists	55	32-40
Consultants	26	45-56

Table IV: Comparison of TIPS pre- and post-test score

	TIPS		Pre-Test	Post-Test	Improvement Score (%)	p-value
1	Time of dystocia to call for Help	Midwives	0.313	0.738	136.23	<0.001
	(1 mark)	Medical officers	0.266	0.445	67.65	<0.001
		Specialists	0.164	0.291	77.78	0.02
		Consultant	0.231	0.346	50.0	NS
2	McRoberts's manoeuvre	Midwives	1.21	1.83	51.55	<0.001
	(2 marks)	Medical officers	1.31	1.95	48.81	<0.001
		Specialists	1.56	2	27.91	<0.001
		Consultant	1.34	1.84	37.1	<0.001
3	Suprapubic pressure	Midwives	0.59	1.77	198.32	<0.001
	(2 marks)	Medical officers	0.91	1.68	84.62	<0.001
		Specialists	1.30	1.92	47.22	<0.001
		Consultants	0.69	1.65	139.1	<0.001
4	Delivery of the posterior arm	Midwives	0.433	2.46	467.15	<0.001
	(4 marks)	Medical officers	1.289	3.164	145.45	<0.001
		Specialists	2.12	3.6	69.23	<0.001
		Consultants	1.34	3.07	133.3	<0.001
5	Total Score	Midwives	2.55	6.77	165.51	<0.001
	(9 marks)	Medical officers	3.78	7.25	91.73	<0.001
		Specialists	5.16	7.82	51.41	<0.001
		Consultants	3.62	6.88	90.43	<0.001

NS- Not significant.



The data are expressed as the median ± SME (standard error of the mean). Data were compared by Kruskal-Wallis test. P-value < 0.05 considered significant.

Fig. 1: Comparisons of TIPS pre- and post-score among groups

There was statistically significant improvement of post-test TIPS score seen in all four groups of HCWs in all the skills assessed.

The percentage of improvement scores (Table IV) showed that cognitive skill for the noting of time and call for help component, midwives showed TIPS improvement score (136 %). This is the highest improvement after training among all four groups whereas consultants showed least improvement of (50 %). In psychomotor skills of directed suprapubic pressure component, midwives and consultants group showed improvement of (198%) and (139%). In component of delivering the posterior arm, midwives showed TIPS improvement score of (467%), medical officers (145%) and consultants (133%) and specialist (69%). Overall, the total score the specialists showed least improvement of (51%) followed by consultants and medical officers (90%) and (91%) and midwives highest (165 %).

Analysis and comparison between various groups is shown in Figure 1, all scores for TIPS components, with the exception of note the time of dystocia before TIPS, were significantly different across all four groups. In noting the time of dystocia post TIPS, midwives significantly did better compared to medical officers, specialists and consultants. For McRobers Manoeuvre, scores for midwives were significantly lower compared with medical officers and specialists post TIPS and there was improvement after training but there was no significant difference among all groups. Pre-score and post score for suprapubic pressure in specialist was significantly higher as compared to the other groups.

For posterior arm component, the scores were significantly higher in specialists in pre- and post-TIPS as compared to other groups. There is a considerable difference in the pre-test score between specialist and the midwives because the specialists were trained in the residency training programme on complicated deliveries. However, from the midwifery perspective, their professional training largely centres on management of uncomplicated or low risk deliveries. Although shoulder dystocia is part of most midwifery curricula, the emphasis is significantly less compared to doctors in their residency training. Total TIPS score improved significantly among midwives, medical officers and consultants followed by specialists.

DISCUSSION

Shoulder dystocia is unpredictable and unpreventable and therefore all obstetric healthcare professional should undergo training in the management of shoulder dystocia. The Royal College of Obstetricians and Gynaecologist & Royal College of Midwives recommends all birth attendants to undergo annual shoulder dystocia skills-drills to prevent clinical negligence suits as a maternity standard. In accordance with that, we have shown that simulated shoulder dystocia training would improve the knowledge, confidence and management of health care providers in managing this emergency.[7-10,11-12]

Simulation lab and mannequins are mostly available in the Malaysian universities where undergraduate and postgraduates undergo training. This is not accessible to general health care providers who may be faced with this emergency. The Ministry of Health Malaysia has invested in obstetric emergencies simulation training which are minimal where Malaysian midwives and Ministry of health doctors undergo training few times a year. ICOE is a structured, standardized and validated course conducted by OGSM in Kuala Lumpur, regularly since 2014. Our dataset addresses the current gap in the current literature where most researchers have tested participants in the training

programme or the resident physicians practicing in the universities but not the general maternity HCP.[9-11] Hence, our objective was to assess the ICOE course participants psychomotor and cognitive skills in management of shoulder dystocia module using TIPS pre-test and post-test score after a short simulation training.

This study of shoulder dystocia skills training module and testing among Malaysian HCPs demonstrated there was a significant improvement of individual post-test skills after short simulation training using high fidelity mannequins. The pre-test TIPS score among all groups were sub optimal to manage this emergency due to an inadequate training and perception of the clinical emergency. The consultant group was generally expected to perform better due to long working clinical experience. We noted their pre-test score were generally suboptimal due to the lack of routine practice of these psychomotor and cognitive skills. Similarly, other studies also have demonstrated this improvement in the management of shoulder dystocia skills and neonatal outcomes after simulation training.[1,2,6,9,13]

As part of the communication skill assessment, which is noting the time of dystocia and calling for help, the consultant group did not show much improvement after training. The consultant group were the senior HCP often called by junior HCP during emergency and this group lacked the skill of involving multidisciplinary team. The midwives improved the most as this emergency is often encountered and practiced by them. For communication scores Goffman et al found junior attending physicians scored significantly higher than senior attending physicians pre training but both groups improved in communication score post training. However, the same group assessed and noted that there was no improvement of documentation of time and date in the delivery notes after training similar to our finding.[10,11]

All four groups improved their TIPS scores in directed suprapubic pressure and Mc Roberts manoeuvre but in the delivery of the posterior arm, midwives improved the most 467%, followed by medical officers 145% and consultants 133%. For midwives this was the new skill trained, hence the marked improvement. Medical officers and consultants performed similarly in this internal manoeuvre, which demonstrated that consultants even though they are qualified and experienced can improve their skill further. This skill is often lost due to lack of practice and rare occurrence. On the contrary, Goffman et al found no significant difference between junior and senior attending physicians pre and post simulation training.[10]

In comparison of total score among the four groups, specialist pre-training skills were better compared to consultants and medical officers, but they showed marginal improvement after training which is due to lack of clinical practice.

We acknowledge the limitations of this observational study where convenient sampling was used. The participants who attended the ICOE training were only assessed, hence there is non- normal distribution of data, the consultant group was small consisting of only 4.2% of study sample. There were different pathways of training for each HCP who have different knowledge and different work settings. During the two days of intensive training, multiple breakout stations were simulated and tested. Apart from shoulder dystocia, TIPS for other skills were also conducted simultaneously, this permitted only limited duration. Hence, delivery of posterior arm was only assessed and other internal rotational manoeuvre like the Wood Screw and reverse Wood's screw manoeuvre were omitted. These manoeuvres had success rate of 72% with less fracture humerus and brachial plexus injury.[13-15] Assessment for complications like obstetric anal sphincter injury and postpartum haemorrhage were taught but not tested.

Malaysian HCPs TIPS pre-test management of shoulder dystocia score is below average. These similar findings have been reported by others; hence our findings clearly illustrate that the management of shoulder dystocia could be improved in all HCPs when presented with such simulation training at regular intervals. National training recommendations in shoulder dystocia skills needs to be revisited. This is to determine the need for further training of all healthcare professionals dealing with this emergency and there by developing a more comprehensive timed skills training in obstetrics emergencies utilizing all available resources in the country.[16-17] Pre-training of TIPS in the management of shoulder dystocia emergency among participants of ICOE were suboptimal. Simulation based skills training in the management of shoulder dystocia improved TIPS of all participants i.e., Malaysian Health care Professionals. Midwives benefited the most followed by medical officers and Consultants. However, Specialist also required to attend and improve their technical and non-technical skills. Simulation based training is a valuable educational tool allowing hands on practice with appreciation of correct technique in the management of shoulder dystocia manoeuvres. It is important to evaluate whether the trained HCPs retain their knowledge and skills in 6 and 12 months and whether such training resulted in reduction of fetal and neonatal morbidity in the centres where the training was introduced. We believe the current study is the first step and this would be followed by assessment of retention of knowledge and skills and whether this resulted in better clinical outcome.

CONCLUSION

ICOE shoulder dystocia simulation module training improved the psychomotor and cognitive skills in the management of delivery of shoulder dystocia.

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ORIGINAL ARTICLE

Identifying predictors of worsening glycaemic outcomes in prediabetes: a two-year cohort study in Terengganu, Malaysia

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ABSTRACT

Introduction: Prediabetes is a critical stage preceding diabetes mellitus (DM) which is also associated with an elevated risk of developing DM and related complications. Addressing predictors that influence the progression or regression of glycaemic outcomes in prediabetic individuals can enhance intervention strategies. This study aims to identify key predictors of glycaemic progression among adults with prediabetes in Terengganu, Malaysia.

Materials and Methods: A retrospective cohort study was conducted involving 592 prediabetic adults from 28 health clinics in Terengganu between January 2019 and June 2023. Participants were selected based on oral glucose tolerance test (OGTT) results indicating prediabetes. Sociodemographic, medical background, and clinical data, including body mass index (BMI), blood pressure, fasting blood sugar (FBS), and lipid profiles, were extracted from medical records. Glycaemic outcomes were classified into three categories: reversion to normoglyacemia, persistent prediabetes, or progression to DM, based on glycated haemoglobin (HbA1c) levels taken within two years of follow-up. Ordinal logistic regression analysis was used to identify the significant predictors influencing these outcomes.

Results: Analysis showed age, BMI, underlying dyslipidaemia, FBS, and triglyceride levels as significant predictors of glycaemic progression. Specifically, each additional year of age and each one-unit increase in BMI raised the likelihood of progression to DM by 3% and 6%, respectively. Participants with dyslipidaemia were noted to have a 67% higher risk of worsening glycaemic status, while increases in FBS and triglyceride levels were associated with 65% and 34% greater odds of diabetic progression, respectively.

Conclusion: This study identifies critical predictors of glycaemic outcomes in prediabetic adults, emphasizing the role of age, BMI, dyslipidaemia, FBS, and triglycerides in the disease progression. These findings support the development of targeted interventions that address these risk factors to curb diabetes progression in high-risk individuals, contributing valuable insights into diabetes prevention strategies tailored for Malaysian populations.

KEYWORDS:
Blood glucose, hyperglycaemia, prediabetic state, Diabetes Mellitus, cohort studies, risk factors, logistic models

INTRODUCTION

Diabetes mellitus (DM) ranks among the top ten global causes of mortality, accounting for over 80% of premature deaths associated with other noncommunicable diseases.[1] The incidence of diabetes has risen to epidemic proportions worldwide, especially in low- and middle-income countries.[2] Prediabetes is a state of intermediate hyperglycaemia which has been one of the major contributors to this trend.[3] Diagnosis of prediabetes is either impaired fasting glucose (IFG), and/or impaired glucose tolerance (IGT), or glycated haemoglobin (HbA1c) levels between 5.7% and 6.4%.[4] 25% prediabetes patients progressed to diabetes within three to five years, with lifetime progression rates reaching up to 70%.[5] Prediabetes carries a 10% to 40% higher risk of cardiovascular complications than normal glucose levels.[6,7] Analysis of the Framingham Heart Study found that women with IFG had a 2.5-fold higher risk of coronary heart disease, almost equal to that of women with diabetes.[6] This suggests that the early stages of glucose dysregulation, even before the onset of diabetes, can lead to substantial cardiovascular risk, although the direct causality is remained debatable.[8] Beside, prediabetes significantly increases the risk of early-stage neuropathy and nephropathy, with evidence showing early nerve dysfunction, such as autonomic and sensory neuropathy, as well as kidney damage, including microalbuminuria, even before the onset of diabetes.[5] Therefore, preventing the progression of prediabetes is critical, as it involves multiple organ complications, emphasizing the importance of early intervention to reduce the overall burden of chronic diseases.[5]

The International Diabetes Federation (IDF) reported that the global prevalence of prediabetes increased from 4.4% in 2010 to 15.5% in 2019, with projection to 8.6% of the adult by

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2045.[9] In United State (US), Rooney et al. reported that 9.1% of adults worldwide met the criteria for IGT, with significant regional variations.[3] This growing prevalence highlights the importance of public health interventions, as nearly 40% to 70% of individuals with IFG progress to diabetes without effective prevention strategies. According to the National Health and Morbidity Survey (NHMS), diabetes prevalence among adults increased from 13.4% in 2015 to 15.6% in 2023.[10] In Terengganu, overall diabetes rates surpass the national average, climbing from 18.6% in 2015 to 20.5% in 2019.[11] A local research conducted in Penang further highlights the issue, with 10.1% of adults diagnosed with prediabetes and 19.6% with diabetes.[12] Although conversion rates from prediabetes to diabetes vary across studies and populations, annual progression rates typically ranges between 5% and 10%. Major studies in US and Japan have reported similar trends.[13-15] Meta-analyses indicate that Asians are nearly twice as likely to develop diabetes within five years compared to individuals of European descent.[16] Long-term cohort studies suggest that between 40% and 50% of individuals with prediabetes may remain in a persistent prediabetic state.[17,18]

Several factors are known to influence the transition from prediabetes to diabetes. Age, obesity, and elevated triglyceride levels are associated with increased progression risk, while weight loss and lower systolic blood pressure (BP) promote reversion to normoglycaemia.[18] Additionally, individuals with higher baseline fasting blood sugar (FBS) or HbA1c levels more or equal to 6.0% are more likely to progress to diabetes.[16,17,19] Existing evidence supports the effectiveness of lifestyle interventions and also the use of metformin in prediabetes to reduce the risk of progression to DM.[8,20,21] A study done in the United States concluded that prediabetes contributes significantly to healthcare costs due to the impact of macrovascular comorbid condition and complications as well as productivity loss, requiring substantial resources for long-term management. These findings underscore the financial strain on healthcare systems and emphasize the importance of early screening and interventions to prevent the progression of prediabetes to DM.[22]

Despite the extensive body of international research, there is a significant gap in understanding prediabetes outcomes and predictors within the Malaysian context. Regional studies are limited, especially in semirural states like Terengganu, which have distinct sociodemographic and healthcare characteristics. This lack of localized data makes it challenging to develop targeted interventions that are culturally relevant and context-specific. This study aims to address this knowledge gap by identifying various key predictors of three glycaemic outcomes; reversion to normoglycaemia, persistent prediabetes and progression to DM, focusing on sociodemographic factors, medical background, and clinical indicators within two years follow-up. The two-year window offers a crucial opportunity to detect early trends in progression and reversion, which may shape intervention programs before irreversible metabolic changes occur. The findings from this study will help the development of more effective prevention strategies tailored to the local population to curb the rising burden of diabetes in Malaysia.

MATERIALS AND METHODS

This study is a retrospective cohort study conducted among 705 adults with prediabetes attending 28 health clinics comprising of 15 health clinics in urban and 13 health clinics in rural areas of Terengganu state from January 2019 to June 2023. While this distribution allows for the inclusion of participants from both urban and rural communities, the generalizability of the findings may be limited. Terengganu is a predominantly east-coast state in Malaysia with a unique sociodemographic profile characterized by a higher proportion of rural communities, distinct cultural practices, and healthcare access challenges that differ from more urbanized regions such as Kuala Lumpur.

The largest required sample size was based on smoking predictor using two-proportion formula, with a proportion of progression among former smokers (P0) at 19.4% and among current smokers (P1) at 26.4%.[18] With a significance level of 0.05 and study power of 80%, the required sample size was 586, which increased to 733 to accommodate a potential 20% dropout rate. The inclusion criteria include adults aged 18 and above diagnosed with prediabetes based on abnormal oral glucose tolerance test (OGTT) as per local guideline.[4] The exclusion criteria were a prior diabetes diagnosis, missing HbA1c results during follow up, and defaulted follow-up within two years after diagnosis of prediabetes. No probability sampling was applied due to limited number of eligible patients and high potential of loss to follow up.

Measurement tools

Data were retrieved from the medical records of adult prediabetes patients in the selected health clinics, in which they were tracked over a two-year follow-up period, started from the day of diagnosis made for each participants (Figure 1). The data retrieval was conducted by two trained healthcare professionals who cross-referenced each patient's medical records to ensure consistency in the information gathered and resolve any discrepancies through consensus, ensuring that all data entries were accurate. Data were recorded using a structured proforma to minimize errors and ensure uniformity in documentation.

The dependent variable was identified as the glycemic status during follow-up, and categorised as such; normoglycaemia, persistent prediabetes, or diabetes mellitus. The glycaemic status was determined by latest available HbA1c levels taken at least six months after diagnosis, up to two years of follow-up. Due to varying follow-up schedules during the COVID-19 pandemic, patients did not return for assessments at consistent time intervals, resulting in differences in the timing of HbA1c measurements taken during the follow-up period. Independent variables include sociodemographic information (e.g., age, gender, marital status, employment, smoking status), medical background (e.g., underlying hypertension, underlying dyslipidaemia, and family history of diabetes), and clinical parameters (e.g., weight, body mass index (BMI), OGTT results, cholesterol levels during visit 1, and systolic and diastolic BP at diagnosis (visit 1) as well as during follow-up (visit 2).

Variable definitions

1. Normoglycaemia: Prediabetes patients who reverted to normoglycaemia within two years follow-up based on one repeated HbA1c (equal or less than 5.6%).[4]
2. Persistent prediabetes: Prediabetes who remained at prediabetes state within two years follow up based on repeated HbA1c range from 5.7% to 6.2%.[4]
3. Diabetes mellitus (DM): Those who progressed from prediabetes to DM based on repeated HbA1c of 6.3% or more within two years of follow-up.[4]
4. Family history of DM: Those who have first-degree family history of DM.
5. Smoking status: Those who were recorded as a smoker in the prediabetes record.
6. Underlying hypertension: Those with pre-existing hypertension, with or without anti-hypertensive medication.
7. Underlying dyslipidaemia: Those with pre-existing dyslipidaemia, with or without lipid-lowering agent.
8. Weight: participants' body weight in Kg recorded at diagnosis of prediabetes (visit 1).
9. Body mass index (BMI): BMI kg/m2 recorded at diagnosis of prediabetes (visit 1).
10. Fasting blood sugar (FBS): level of venous blood glucose in fasting state taken at diagnosis (visit 1).
11. 2-hour postprandial (2-HPP): level of venous blood glucose after two hours of taking a standard 75-gram of glucose solution (visit 1).
12. Level of systolic blood pressure (SBP): SBP level in mmHg recorded at diagnosis of prediabetes (visit 1).
13. Level of diastolic blood pressure (DBP): DBP level in mmHg recorded at diagnosis of prediabetes (visit 1).
14. Cholesterol level: total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and High-density lipoprotein (HDL) cholesterol taken at diagnosis (visit 1).

Statistical analysis

Statistical analyses were performed using STATA, focusing on the ordinal logistic regression model. Descriptive statistics were initially applied to provide an overview of the dataset, with further analysis conducted to assess the relationships between prediabetes outcomes and the predictors. The variables used in the analysis were chosen based on univariable analysis with a p-value threshold of <0.25. The significant variables identified were included in the multivariable analysis. The continuous variables were treated as linear after testing for linearity using the multivariable fractional polynomial method. The assumptions for ordinal logistic regression were then assessed, including multicollinearity, interactions, similarity between the proportional model and the unconstrained baseline logit model, and proportional odds assumption. The overall fit of the model was evaluated using the Hosmer-Lemeshow test, Pearson chi-square test, correctly classified percentage, and the area under the receiver operating characteristic (ROC) curve (AUC).

Ethical approval

The present study protocol was reviewed and approved by the Universiti Sultan Zainal Abidin (UniSZA) Research Ethics Committee (approval No. UniSZA/UHREC/2023/523) and Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-23-00389-BM8)

RESULTS

A total of 592 participants had complete data available for inclusion and were included in the analysis. The reduced sample size was due to missing or incomplete records, which still exceeded the original required sample size of 586, ensuring sufficient power for the analysis. Out of total 592 participants, 25.0% (n=148) reverted to normoglycemia, 59.1% (n=350) remained stable with prediabetes, and 15.9% (n=94) progressed to DM within the two-year follow-up. Majority of participants were female (68.75%), unemployed (69.43%), non-smoker (88.85%), with underlying history of hypertension (83.78%) and dyslipidaemia (81.93%). Median age was 61 years old (IQR=51.5-69.0) as in Table I.

Univariable and multivariate analysis

From the univariable analysis, several variables met the inclusion criteria for the multivariable model (p<0.25), including age, sex, occupation, underlying hypertension, underlying dyslipidemia, FBS, triglyceride level, BMI, systolic blood pressure at visit 2, and DBP at visit 2. These factors were subjected to further multivariable ordinal logistic regression analysis. The results demonstrated that age, BMI, underlying dyslipidemia, FBS level, and triglyceride level were significant independent predictors of diabetes progression (Table II). Controlling for other factors, for each additional year of age, the odds of having a worse glycaemic status (progressed from normoglycaemia to prediabetes or from prediabetes to DM) increase by 3% (OR=1.03, 95% CI=1.01 to 1.05, p=0.003). Individuals with underlying dyslipidemia have 67% higher odds of having a worse glycaemic status (progressed from normoglycaemia to prediabetes or from prediabetes to DM) compared to those without dyslipidemia (OR=1.67, 95% CI=1.05 to 2.63, p=0.03). For each one-unit increase in BMI, the odds of having a worse glycaemic status increase by 6% (OR=1.06, 95% CI=1.03 to 1.10, p< 0.001). For each unit increase in FBS, the odds of having a worse glycaemic status (progressed from normoglycaemia to pre-diabetes or from pre-diabetes to DM) increase by 65% (OR=1.65, 95% CI=1.23 to 2.21, p=0.001). For each one-unit increase in triglyceride levels, the odds of having a worse glycaemic status progressed from normoglycaemia to pre-diabetes or from pre-diabetes to DM) increase by 34% (OR=1.34, 95% CI=1.05 to 1.72, p=0.023).

Model diagnostics and assumptions

The model's assumptions were thoroughly checked. Multicollinearity was assessed using the Variance Inflation Factor (VIF). All variables included in the regression model had VIF values below 5, indicating no significant multicollinearity. The top three highest VIF values were for Age (1.93), sex (1.81), and total cholesterol (1.89), with other variables ranging between 1.05 and 1.92. No clinically significant interaction terms were identified. The proportional odds assumption was satisfied (p=0.501) based on the Brant test of parallel regression assumption, confirming that the relationship between the independent variables and the log odds of progressing to higher levels of the outcome (normoglycaemia to prediabetes, prediabetes to DM) was constant across the levels. The Bayesian Information Criterion (BIC) difference of 62.135 indicated strong support for the saved model, with a p-value of 0.272, confirming no significant difference between the proportional and unconstrained baseline models. The first

Table I: Sociodemographic, medical background and clinical parameters of participants by glycaemic outcomes (n=592)

Characteristics	Normoglycaemia, n=161 n (%)	Prediabetes, n=337 n (%)	Diabetes Mellitus, n=94 n (%)
Age (years)[a]	59 (45-68)	62 (53-69)	62 (54-69)
Sex			
Male	42 (26.09)	110 (32.64)	33 (35.11)
Female	119 (73.91)	227 (67.36)	61 (64.89)
Occupation			
Unemployed	119 (73.91)	228 (67.66)	64 (68.09)
Employed	42 (26.09)	109 (32.34)	30 (31.91)
Smoking status			
Non-smoker	144 (89.44)	301 (89.32)	81 (86.17)
Smoker	17 (10.56)	36 (10.68)	13 (13.83)
Hypertension			
No	33 (20.50)	54 (16.02)	9 (9.57)
Yes	128 (79.50)	283 (83.98)	85 (90.43)
Dyslipidaemia			
No	46 (28.57)	50 (14.84)	11 (11.70)
Yes	115 (71.43)	287 (85.16)	83 (88.30)
Family history of diabetes			
No	100 (62.11)	218 (64.69)	55 (58.51%)
Yes	61 (37.89)	119 (35.31)	39 (41.49%)
BMI[a]	26.5 (23.5-29.4)	27.9 (24.4-31.1)	28.3 (25.7-32.4)
FBS[a]	5.8 (5.3-6.2)	6 (5.6-6.3)	6.2 (5.8-6.4)
2-HPP[a]	8.8 (8.0-9.8)	8.9 (8.0-9.8)	8.6 (7.8-9.8)
Total cholesterol[a]	5.6 (4.7-6.3)	5.3 (4.7-6.3)	5.7 (4.7-6.5)
Triglycerides[a]	1 (0.8-1.4)	1.2 (0.86-1.52)	1.3 (0.91-1.80)
HDL cholesterol[a]	1.49 (1.26-1.75)	1.4 (1.2-1.66)	1.37 (1.2-1.64)
LDL cholesterol[a]	3.46 (2.6-4.2)	3.3 (2.69-4.2)	3.55 (2.8-4.5)
SBP (Visit 1)[a]	137 (126-148)	136 (127-145)	137 (129-146)
DBP (Visit 1)[a]	80 (72-87)	80 (73-86)	81 (73-85)
SBP (Visit 2)[a]	134 (126-142)	134 (126-142)	136 (126-149)
DBP (Visit 2)[a]	78 (73-85)	80 (74-86)	80 (73-85)
HbA1c level (Visit 2)[a]	6.0 (5.7-6.3)	6.1 (5.7-6.3)	6.2 (5.9-6.5)

[a] Data presented in median (interquartile range, IQR)
SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg
BMI, body mass index in Kg/m^2; FBS, fasting blood sugar in mmol/L; 2-HPP, 2-hour postprandial in mmol/L; Total cholesterol, triglycerides, LDL, low density lipoprotein; HDL, high density lipoprotein in mmol/L; HbA1c in mmol/L

model, with outcomes regression to normoglycaemia and persistent prediabetes, showed a Hosmer-Lemeshow p-value of 0.0518 and Pearson chi-square p-value of 0.3687. For the second model, which included outcomes regression to normoglycaemia and progressed DM, the Hosmer-Lemeshow p-value was 0.5059 and, the Pearson chi-square p-value of 0.1042.

Area under the receiver-operating characteristic curve (ROC) curve
The discriminatory power of the model was assessed using the area under the ROC curve. For the first model comparing normoglycaemia to persistent prediabetes, the Area Under the curve (AUC) was 0.6861, indicating acceptable discrimination. The second model, comparing normoglycaemia to DM, showed an AUC of 0.7810, suggesting good discrimination. These results implied that the model performed reasonably well in distinguishing between different stages of diabetes progression (Figure 2).

Final model
The final model included the significant factors of age, BMI, FBS levels, underlying dyslipidaemia, and triglyceride levels. These variables, along with adjusted odds ratios and 95% confidence intervals, are presented in Table II. The model was able to correctly classify 68.3% of the cases for normoglycaemia and persistent prediabetes, and 71.0% for normoglycaemia and progression to DM, confirming its reliability.

DISCUSSION

This study revealed that more than half (59.1%) remained in the prediabetic state, 15.9% progressed to DM, while only 25.0% reverted to normoglycaemia within the two-year follow-up. Similar results were found in previous studies conducted by Shang et al., Bennasar et al. and Wuttisathapornchai et al.[17,18,28] While these prevalence findings provide valuable context, the primary focus of this study is to identify predictors of glycaemic progression among prediabetic adults. Our findings are consistent with previous research, particularly highlighting the significant roles of age, BMI, FBS levels, dyslipidaemia, and triglyceride levels in predicting the progression from prediabetes to DM. The final multivariate model developed in this study further supports these predictors, providing a reliable framework for identifying high-risk individuals who may benefit from early intervention.

Table II: Predictors of prediabetes outcomes (regression to normoglycemia, persistent prediabetes and progression to DM) within a two- year follow-up by ordinal logistic regression

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Sex				
Female	0.75 (0.53, 1.05)	0.097	0.88 (0.57, 1.38)	0.585
Male (Ref)	Ref	-	Ref	-
Age (years)	1.02 (1.01, 1.04)	0.001	1.03 (1.01, 1.04)	0.003
Occupation				
Employed	1.23 (0.88, 1.73)	0.226	1.16 (0.74, 1.82)	0.511
Unemployed (Ref)	Ref	-	Ref	-
Smoking				
Yes	1.19 (0.72, 1.97)	0.499	-	-
No (Ref)	Ref	-	-	-
Underlying Hypertension				
Yes	1.62 (1.06, 2.46)	0.026	0.74 (0.44, 1.22)	0.243
No (Ref)	Ref	-	Ref	-
Underlying dyslipidaemia				
Yes	2.28 (1.51, 3.44)	<0.001	1.67 (1.05, 2.63)	0.028
No (Ref)	Ref	-	Ref	-
Family history DM				
Yes	1.05 (0.75, 1.46)	0.756	-	-
No (Ref)	Ref	-	-	-
BMI	1.06 (1.03, 1.09)	<0.001	1.06 (1.02, 1.11)	<0.001
FBS	1.89 (1.44, 2.49)	<0.001	1.65 (1.22, 2.21)	0.001
2 -HPP	0.96 (0.85-1.07)	0.451		
Total cholesterol	0.99(0.90-1.09)	0.782		
Triglycerides	1.48 (1.17, 1.89)	0.001	1.34 (1.04, 1.72)	0.023
LDL	1.07 (0.94-1.23)	0.310		
HDL	0.94 (0.71-1.23)	0.648		
SBP (Visit 1)a	0.99 (0.98, 1.01)	0.538	-	-
DBP (Visit 1)a	1.00 (0.98, 1.01)	0.618	-	-
SBP (Visit 2)a	1.01 (0.99, 1.03)	0.209	0.99 (0.98, 1.01)	0.387
DBP (Visit 2)a	1.01 (0.99, 1.03)	0.185	1.02 (1.00, 1.04)	0.094

SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg
BMI, body mass index in Kg/m^2; FBS, fasting blood sugar in mmol/L; 2-HPP, 2-hour postprandial in mmol/L; Total cholesterol in mmol/L, triglycerides in mmol/L, LDL, low density lipoprotein in mmol/L; HDL, high density lipoprotein in mmol/L

Our study's findings on the role of age in the progression of prediabetes to DM aligned with previously reported data. DeJesus et al. identified age as an independent predictor of diabetes progression, while Liu et al.[16, 23] further reinforced this by demonstrating a significant difference in age between those who progressed to DM and those who did not in a two-year cohort of 14,231 Chinese participant. These studies emphasized the role of age as a key determinant in the transition from prediabetes to DM in certain populations. However, some studies did not find age as a significant predictor.[18,24,25] For instance, Rooney et al. reported progression to DM among prediabetic adults was uncommon (8%) over a five-year follow-up, with the majority either reverted to normoglycaemia (44%) or passed away (16%).[24] Similarly, Ligthart et al. reported that the lifetime risk of diabetes progression reduced with advancing age.[25] This variation in findings may be explained by the differences in study populations, definitions of prediabetes, follow-up durations, and lifestyle factors, which influence the reported risks of diabetes progression in older adults.

A population-based study conducted over a 12-year follow-up period in older adults in Sweden concluded the importance of BMI and weight changes as key factors influencing the progression of prediabetes.[17] In this study, obesity significantly increased the risk of progressing to DM, while weight loss was associated with a greater likelihood of reverting to normoglycemia. Similarly, in our study, higher BMI is a significant predictor in which for each one-unit increase in BMI, the odds of having worse glycaemic status increase by 6%. This finding is also in line with a few other studies.[8,16,18,19] The strong association between increased body weight and the development of DM can be explained by several physiological mechanisms. Greater adiposity, particularly central obesity, plays a significant role in promoting insulin resistance. The adipocytes release free fatty acids and inflammatory cytokines, which disrupt the insulin signalling pathways leading to worsening hyperglycaemia and accelerating the progression from prediabetes to DM.[26] These consistent findings highlight the critical role of addressing obesity in diabetes prevention strategies, thus reinforces the need for targeted interventions aimed at weight management.

Our study did not find elevated BP or underlying hypertension to be significant predictors of progression to diabetes. This is consistent with the findings of Yeboah et al.[14] who also reported that BP was not significant predictors of diabetes progression. However, a longitudinal study done in China demonstrated that individuals with concurrent prediabetes and hypertension exhibiting a 6.37-fold higher risk of developing DM compared to those without these conditions.[28] On the other hand, Shang et al. identified that lower SBP and the absence of heart disease were associated with reversion to normoglycaemia.[17] This suggests that effective blood pressure control may offer an additional

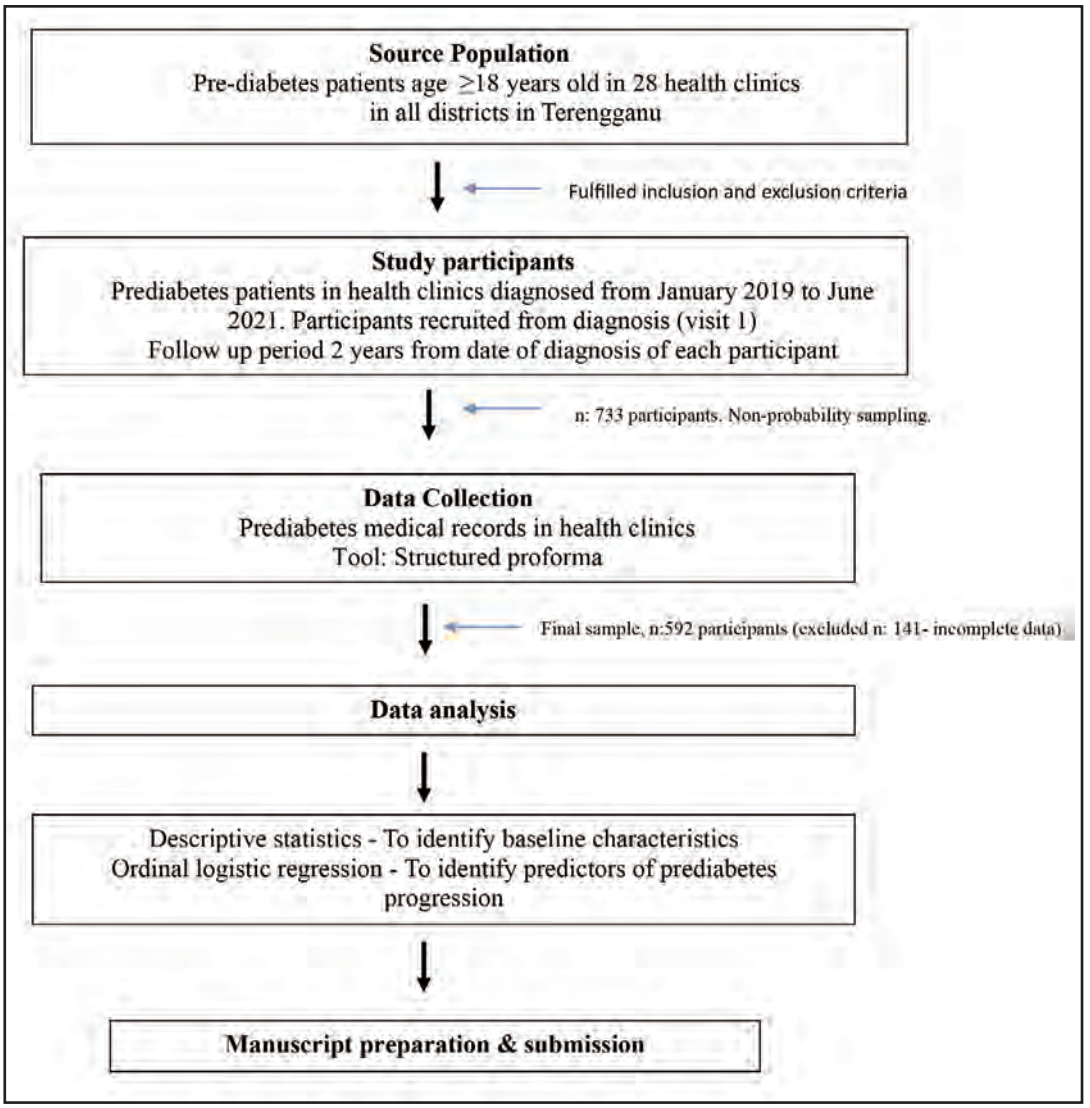

Fig. 1: Study flowchart

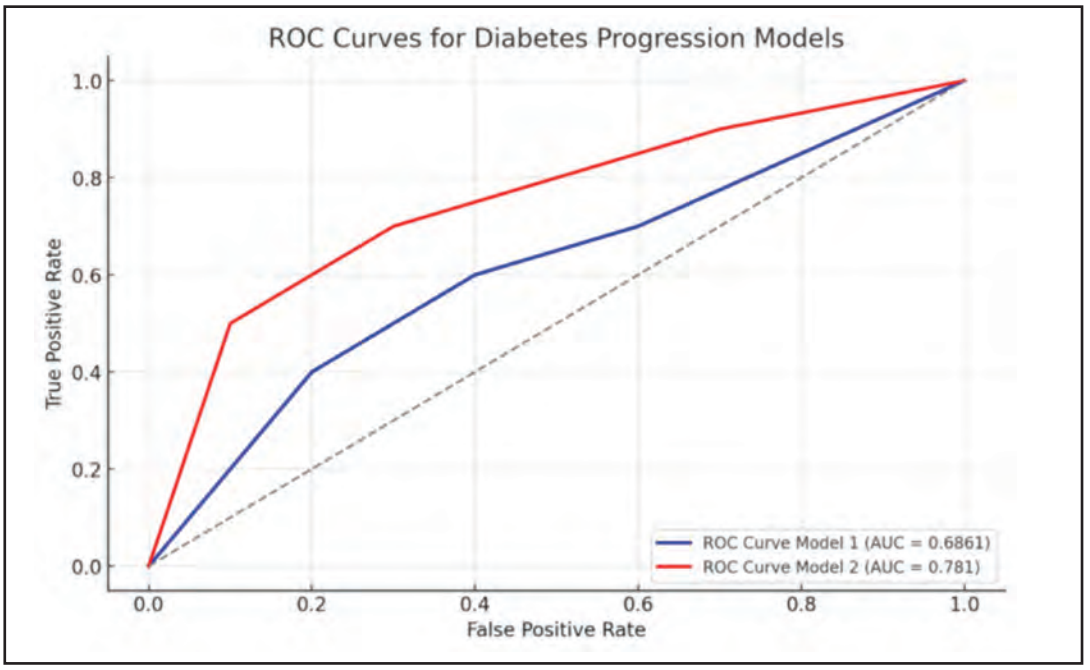

Fig. 2: Area under the curve (ROC)

approach to reducing insulin resistance and supporting glycaemic stability, further highlighting the importance of addressing cardiovascular factors in prediabetes management. In contrast, our findings suggest that hypertension alone might not strongly influence diabetes risk in this cohort. This difference could be due to variations in population characteristics, such as differences in lifestyle, healthcare access, or genetic predispositions. Additionally, the shorter follow-up period in our study may have limited the observation of the long-term effects of hypertension on glycaemic progression.

Our study's findings on the significant role of FBS level in the progression of prediabetes to DM aligned with those of DeJesus et al., Janghorbani et al., and Wutthisathapornchai et al. who also identified baseline FBS levels as a significant independent predictor of diabetes progression.[16,19,28] In a retrospective cohort study, DeJesus et al. found that each unit increase in baseline fasting glucose was associated with a 12% increase in the risk of diabetes progression, a trend that parallels the progression patterns observed in our cohort.[16] Individuals with FBS level in the prediabetic range (more or equal to 5.6 mmol/L) face a significantly higher risk of progressing to DM due to hepatic insulin resistance, a key factor in worsening glucose regulation.[5] Furthermore, numerous diabetic risk prediction models include FBS as a core component, owing to its strong association with diabetes progression. Although various models, ranging from simple clinical tools to complex machine learning algorithms, have been proposed, none have gained universal acceptance.[5] Meanwhile, in our study, abnormal 2-HPP glucose level or IGT alone was not a significant predictor of diabetes progression. This aligns with previous research, which found that individuals with IFG alone or combined IFG and IGT were more prone to develop DM than those with isolated IGT.[5,19,29] A study conducted by Loiuse and Clude highlighted the different contributions of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) to HbA1c levels.[30] It found that PPG had a lesser influence in predicting diabetes in individuals with higher HbA1c levels (more than 7.3%). That is why FBS level, which primarily reflects hepatic insulin resistance, serves as a more reliable and stronger predictor of diabetes risk.[5] The consistent identification of FBS as a key predictor in various studies underscores its crucial role in recognizing high-risk individuals who may benefit from early intervention and regular monitoring of blood sugar to reduce their risk of progressing to DM.

Based on our analysis, underlying dyslipidaemia emerged as a significant predictor of diabetes progression, increasing the risk by 67%. This aligns with existing evidence that lipid abnormalities, particularly elevated cholesterol levels, play a role in diabetes progression.[18,19,23] For instance, Liu et al. found significant differences in lipid profiles across three prediabetes outcome groups (progression to DM, persistent prediabetes, and normoglycaemia), suggesting that dyslipidaemia contributes to glycaemic deterioration.[23] However, a few other studies did not find lipid profiles, including total cholesterol and triglyceride levels, to be significant predictors of diabetes progression, reflecting variability in the influence of lipid factors across different populations and study designs.[14,17]

Elevated triglyceride levels was identified as one of the significant predictors of progression from prediabetes to DM in our study, which further supports the role of lipid abnormalities in the deterioration of glycaemic control in prediabetes. This finding is consistent with a few other studies which highlighted that high triglyceride levels contribute to insulin resistance and are often associated with other metabolic abnormalities that accelerate the progression to diabetes.[18,29] However, in contrast to these findings, Yeboah et al.[14] reported that triglyceride levels and other lipid profiles were not significantly different between IFG patients who progressed to diabetes and those who did not during follow-up. This suggests that the impact of triglycerides on diabetes progression may vary across different populations, potentially influenced by other factors like genetic predisposition or insulin resistance, which might play a more prominent role in certain groups.

This study has several limitations. As a retrospective study, it relies on existing medical records, potentially leading to incomplete or inconsistent data. Unmeasured confounding variables such as dietary habits, physical activity, and socioeconomic status may influence diabetes progression but were not included in the dataset due to the retrospective cohort design, which relied on existing secondary data in medical records where such information was unavailable. Besides, the specific population of adults attending health clinics in Terengganu may limit the generalizability of findings to other regions. The inclusion of participants from 15 urban and 13 rural health clinics within the state ensures a balanced representation of community settings; however, the reliance on government health clinics may introduce selection bias. Individuals who receive care from private healthcare providers or those who do not actively engage with the healthcare system may have different predictors of glycaemic progression. Additionally, rural populations often face barriers related to healthcare access, health literacy, and socioeconomic disparities, which may not be present in more urbanized populations. These social determinants of health could influence lifestyle behaviours, treatment adherence, and follow-up consistency, potentially affecting glycaemic outcomes.

Moreover, although the prediabetes population in Terengganu may share some similarities with other Malaysian states, differences in ethnic composition, dietary patterns, and access to health education could contribute to variations in prediabetes prevalence and its key predictors.

As such, while the findings provide crucial insights into predictors of glycaemic progression, they may not be fully generalizable to Malaysia's broader population. Hence, future research should aim to include multiple states with a more diverse sociodemographic profile to improve the generalizability and external validity of the results. Finally, variations in follow-up intervals due to the COVID-19 pandemic could affect the consistency of glycaemic tracking.

CONCLUSION

This study highlights key predictors; age, BMI, dyslipidaemia, FBS, and triglycerides that significantly influence the progression from prediabetes to DM among Malaysian adults. By establishing a local understanding of these

predictors, our study contributes valuable insights to the ongoing efforts on diabetes prevention, emphasizing the importance of early intervention in high-risk individuals as well as developing more proactive diabetes prevention strategies tailored to specific population needs. Such efforts are essential for reducing the clinical and economic burden of diabetes in Malaysia. Future studies could employ a prospective design with extended follow-up periods to capture long-term outcomes and provide a clearer view of glycaemic progression. Additionally, intervention-based research focusing on targeted lifestyle modifications or medication efficacy would help identify effective strategies for high-risk groups.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Evaluation of choroidal thickness in Malay children with myopia

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ABSTRACT

Introduction: This study aims to evaluate the choroidal thickness and its correlation with age, spherical equivalent, and axial length in Malay children with myopia, addressing the limited data available on this topic in Southeast Asia.

Material and Methods: A cross-sectional, hospital-based study was conducted from 2022 to 2024 at Hospital Shah Alam and Hospital Pakar Universiti Sains Malaysia. A total of 109 Malay children aged 7-17 years participated, including 88 with myopia and 21 with emmetropia. Each participant underwent a comprehensive ocular examination, including non-cycloplegic refraction and axial length measurement. Choroidal thickness was assessed using Cirrus SD-optical coherence tomography, with one eye from each subject randomly selected for analysis.

Results: The mean subfoveal choroidal thickness was significantly thinner in myopic children (284.91 µm) compared to emmetropic children (347.62 µm) (p<0.001). Additionally, choroidal thickness varied significantly with the degree of myopia: mild myopia had a mean subfoveal thickness of 319.69 µm, moderate myopia 290.04 µm, and high myopia 225.72 µm, with high myopia showing the thinnest choroid (p<0.001). A significant negative correlation was observed between axial length and subfoveal choroidal thickness, while a positive correlation was found between spherical equivalent and choroidal thickness. No significant correlation was identified between age and subfoveal choroidal thickness.

Conclusion: Malay children with myopia exhibit a thinner mean choroidal layer compared to their emmetropic peers, with the thinnest choroid observed in cases of high myopia. This indicates that thinning of the choroidal vasculature occurs with the increase in axial length and worsening severity of myopia.

KEYWORDS:
choroidal thickness, myopia, axial length, spherical equivalent, children

INTRODUCTION

Myopia has become an alarming epidemic due to its rapidly increasing prevalence over the past three decades, now representing a significant public health challenge. The condition imposes a substantial burden, both in terms of the need for optical correction and the management of visual impairment associated with pathological myopia. Uncorrected myopia negatively impacts school performance, employability, and overall quality of life. Globally, myopia affects approximately 28.3% of the population, with 4.0% classified as high myopia.[1] The prevalence of myopia among children varies across continents, ranging from 0.7% in Saudi Arabia and 1.4% in South America to 7.5% in India and 36.2% in Hong Kong.[2-5] Population-based studies have reported an exceptionally high prevalence of myopia among East Asian children, with the highest rates observed in Taiwan (85.1%), followed by China (80.7% in Beijing) and South Korea (78.8%).[6,7] The highest prevalence of myopia among schoolchildren has been documented in Southeast Asian countries and China, affecting approximately 13.9% of Malay children in Malaysia.[8]

The choroid plays a crucial role in supplying nutrients and growth factors to the retina, and it is likely also involved in predicting biomarkers for axial length changes that correlate with myopia progression.[9] It is believed that before myopia develops, the rapid elongation of the eyeball causes choroidal thinning. This thinning may be associated with reduced choroidal blood flow, potentially leading to scleral ischemia and hypoxia. As a result, the sclera becomes thinner and weaker, which in turn leads to excessive elongation of the eyeball and accelerates the onset of myopia.[10] Thinner choroidal thickness has been reported to correlate with poorer best-corrected visual acuity and associated with various myopic pathological lesions, such as choroidal neovascularization, lacquer cracks, staphyloma, and chorioretinal atrophy.[11]

Choroidal thickness has been shown to be thinner in myopic compared to emmetropic and hyperopic children and adults.[12-16] However, the available studies among children primarily involved very young age with only mild to moderate degrees of myopia. There is limited research focusing on older children and those with a high degree of myopia. The aim of this study was to compare the mean choroidal thickness between emmetropic and myopic children across a wide range of refractive errors and to explore its correlation with age, axial length, and spherical equivalent.

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MATERIALS AND METHODS

This cross-sectional study was conducted at the Ophthalmology Clinics of Hospital Shah Alam and Hospital Pakar Universiti Sains Malaysia, Malaysia, from June 2022 to May 2024. Healthy children aged seven to 17 years with myopia and emmetropia were recruited. The study was conducted in accordance with the Declaration of Helsinki for Human Research and was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/22030159) and the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-01226-MS8). Written consent and assent were obtained from the subjects and their parents.

Children aged seven to 17 years with myopia who attended the Myopia Clinics at both institutions were recruited for the study. The inclusion criteria included full-term myopic children. Age-matched healthy children were prospectively enrolled as controls. Children with any ocular pathology other than myopia, such as glaucoma, corneal scars, optic neuropathy, or those who had undergone ocular surgery or experienced trauma, were excluded. Additionally, patients with myopic maculopathy or chorioretinal scars were also excluded.

Demographic data, including age, gender, education level, and household income, were collected. Comprehensive ophthalmic evaluations were conducted, which included assessments of visual acuity, non-cycloplegic manifest refraction, anterior segment examination, intraocular pressure measurement, and fundus examination. Axial length was measured using the IOL Master (Carl Zeiss Meditec Inc.), a partial coherence interferometer.

The spherical equivalent (SE) was calculated as the sum of the spherical power plus half of the cylindrical power. Myopia was defined as a spherical equivalent refraction worse than -0.5 diopters (D). Participants were categorized into four groups:

- Emmetropia: SE between +1.00D and >-0.50D
- Mild Myopia: SE between -0.50D and -3.00D
- Moderate Myopia: SE between <-3.00D and -6.00D
- High Myopia: SE worse than <-6.00D[1,8]

Spectral-domain optical coherence tomography (SD-OCT) was used to capture high-definition (HD) images of the choroid, utilizing the HD radial mode of the Cirrus HD-OCT instrument (Carl Zeiss Meditec Inc.) to enhance choroidal depth imaging. Choroidal thickness was measured from the outer border of the retinal pigment epithelium to the inner border of the choroidoscleral interface. Measurements were taken across multiple locations: temporal, superotemporal, superior, superonasal, nasal, inferonasal, inferior, and inferotemporal. These measurements were analyzed in three zones:

- Central Foveal Zone: From the foveal center to a 1 mm diameter
- Inner Macular Zone: From the inner 1 mm diameter to the outer 3 mm diameter
- Outer Macular Zone: From the inner 3 mm diameter to the outer 6 mm diameter (Fig. 1).

To minimize the effects of diurnal variation, measurements were conducted between 9:00 a.m. and 1:00 p.m. Only OCT images with a signal strength of six or higher were included in the analysis. Images were centered on the fovea, and only those with clear visualization extending to the choroidoscleral interface were accepted. Choroidal layer measurement was done once manually by a single trained observer. The observer underwent formal training for segmentation of the choroidal layer and measurement of the choroidal thickness.

Data entry and statistical analysis were performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Socio-demographic details and clinical characteristics of the patients were analyzed using descriptive statistics, including frequencies, percentages, means, standard deviations, and ranges. Although data were acquired from both eyes, only one eye was randomly selected from each subject for statistical analysis.

An independent t-test was employed to compare the mean choroidal thickness between myopic and emmetropic Malay children. To examine differences in choroidal thickness across mild, moderate, and high myopia groups, a one-way analysis of variance (ANOVA) was performed. The correlations between mean choroidal thickness and variables such as age, spherical equivalent, and axial length were evaluated using bivariate analyses, including Pearson's and Spearman's correlation tests. Statistical significance was determined at the 5% level ($p<0.05$) for all analyses.

RESULTS

A total of 109 subjects were enrolled in this study. 88 Malay children with myopia and 21 age and gender-matched emmetropic Malay children were included. The spherical equivalent of the children ranged from -15.25 D to +1.00 D. The axial length ranged from 21.73 to 30.19 mm. Table I provides a summary of the demographic and clinical comparisons between the myopia and emmetropia groups. Statistically significant differences were observed between the two groups in terms of mean spherical equivalent and axial length ($p<0.001$).

The subfoveal choroidal thickness of all studied children ranged from 109 to 423 µm with a mean of 296.99 (70.00) µm. The subfoveal choroidal thickness in the myopia group was significantly thinner than the emmetropia group as demonstrated in Table I ($p<0.001$).

Table II presents the comparisons based on the severity of myopia. Patients with high myopia had the thinnest mean choroidal thickness in all zones, followed by those with moderate and mild myopia. A gradual decrease in mean subfoveal choroidal thickness was observed as the degree of myopia increased. Post hoc analysis (Bonferroni) demonstrated in Table III showed a significant difference between mild and high myopia groups in all macula zones. Moderate to high groups showed statistically significant differences in most of the macula zones except in temporal, superior and inferior outer macula zones. However, in mild to moderate group analysis, significant differences were

Table I: Demographic and clinical characteristics between myope and emmetrope (n = 109)

Characteristic	Myopia (n = 88)	Emmetropia (n = 21)	p-value
Age (year), Median (IQR)	10 (4)	9 (4)	[a]0.420
Gender, n (%)			
Male	45 (51.1)	11 (52.4)	[b]0.918
Female	43 (48.9)	10 (47.6)	
Spherical equivalent (diopters), Mean (SD)	-4.76 (3.56)	+0.14 (0.40)	[c]<0.001
Axial length (mm), Mean (SD)	25.02 (1.73)	22.77 (0.60)	[c]<0.001
Subfoveal choroidal thickness (μm), Mean (SD)	284.91 (70.88)	347.62 (35.81)	[c]<0.001

IQR = interquartile range, SD = standard deviation,
[a]Mann-Whitney U test
[b]Pearson Chi-squared test
[c]Independent t-test

Table II: Comparison of choroidal thickness between mild, moderate and high myopia (n = 88)

Zone (μm)	Mild myopia (n = 39) Mean (SD)	Moderate myopia (n = 24) Mean (SD)	High myopia (n = 25) Mean (SD)	F-statistic (df)	*p-value
Subfovea	319.69 (53.77)	290.04 (49.68)	225.72 (75.02)	19.07 (2)	<0.001
Nasal Fovea	297.31 (56.83)	267.08 (46.70)	204.80 (71.56)	18.82 (2)	<0.001
Temporal Fovea	310.44 (53.96)	283.33 (51.76)	217.44 (68.44)	19.89 (2)	<0.001
Superior Fovea	299.41 (53.50)	275.17 (47.18)	205.44 (67.17)	21.74 (2)	<0.001
Inferior Fovea	297.90 (51.59)	273.83 (46.58)	202.56 (69.68)	22.47 (2)	<0.001
Nasal Inner Macula	262.44 (63.24)	224.67 (48.34)	159.76 (61.07)	23.13 (2)	<0.001
Temporal Inner Macula	299.21 (55.14)	263.25 (49.91)	219.68 (58.49)	16.13 (2)	<0.001
Superior Inner Macula	280.77 (46.98)	251.96 (44.79)	200.76 (65.58)	17.79 (2)	<0.001
Inferior Inner Macula	277.13 (48.79)	251.50 (45.89)	195.24 (77.41)	15.46 (2)	<0.001
Nasal Outer Macula	185.05 (53.99)	146.88 (34.69)	97.72 (43.50)	26.93 (2)	<0.001
Temporal Outer Macula	257.77 (51.84)	221.83 (53.23)	205.40 (58.59)	7.82 (2)	<0.001
Superior Outer Macula	245.21 (46.96)	201.38 (64.56)	193.40 (68.38)	7.37 (2)	0.001
Inferior Outer Macula	236.33 (44.46)	199.29 (54.21)	179.24 (69.18)	8.82 (2)	<0.001

*One-way ANOVA test followed by post-hoc multiple comparison test Bonferroni procedure applied

Table III: Comparison of choroidal thickness between mild, moderate and high myopia (n = 88)

Zone (μm)	Mild vs moderate myopia		Mild vs high myopia		Moderate vs high myopia	
	MD (95% CI)	*p-value	MD (95% CI)	*p-value	MD (95% CI)	*p-value
Subfovea	29.65 (-8.10, 67.40)	0.175	93.97 (56.69, 131.25)	< 0.001	64.32 (22.74, 106.90)	0.001
Nasal Fovea	30.22 (-7.15, 67.60)	0.155	92.51 (55.60, 129.42)	< 0.001	62.28 (21.11, 103.45)	0.001
Temporal Fovea	27.10 (-9.57, 63.77)	0.224	93.00 (56.78, 129.21)	< 0.001	65.89 (25.50, 106.29)	<0.001
Superior Fovea	24.24 (-11.35, 59.84)	0.300	93.97 (58.82, 129.12)	< 0.001	69.73 (30.52, 108.93)	<0.001
Inferior Fovea	24.06 (-11.49, 59.62)	0.306	93.34 (60.23, 130.45)	< 0.001	71.27 (32.11, 110.43)	<0.001
Nasal Inner Macula	37.77 (0.43, 75.11)	0.047	102.68 (65.80, 139.55)	< 0.001	64.91 (23.77, 106.04)	0.001
Temporal Inner Macula	35.96 (1.25, 70.66)	0.040	79.53 (45.26, 113.79)	< 0.001	43.57 (5.35, 81.79)	0.020
Superior Inner Macula	28.81 (-4.38, 62.00)	0.111	80.01 (47.24, 112.78)	< 0.001	51.20 (14.64, 87.75)	0.003
Inferior Inner Macula	25.63 (-10.91, 62.17)	0.271	81.89 (45.80, 117.97)	< 0.001	56.26 (16.01, 96.51)	0.003
Nasal Outer Macula	38.18 (8.71, 67.64)	0.006	87.33 (58.23, 116.43)	< 0.001	49.16 (16.70, 81.61)	0.001
Temporal Outer Macula	35.94 (1.60, 70.28)	0.037	52.37 (18.46, 86.28)	0.001	16.43 (-21.39, 54.26)	0.875
Superior Outer Macula	43.83 (6.70, 80.96)	0.015	51.81 (15.14, 88.47)	0.003	7.98 (-32.92, 48.87)	1.000
Inferior Outer Macula	37.04 (2.16, 71.92)	0.034	57.09 (22.65, 91.54)	< 0.001	20.05 (-18.37, 58.47)	0.618

*One-way ANOVA test with post hoc Bonforreni correction.

observed in the nasal and temporal inner and all outer macula zones.

The mean subfoveal choroidal thickness demonstrated a significant positive correlation with spherical equivalent (r=0.67, p<0.001) and negative correlation with axial length (r=-0.63, p< 0.001). However, no significant correlation was found between mean subfoveal choroidal thickness and age (r=0.06).

DISCUSSION

Our study exhibited thinner subfoveal choroid among myopic children compared to emmetropic children. Myopic children also had thinner choroids in most areas of the posterior pole. In our study, the mean subfoveal choroidal thickness in the myopic children aged 7 to 17 years old was 284.91 (70.88) μm which is similar to the study done in Nanchang, Jiangxi, China which recruited myopic Chinese children aged 6 to 16 years old with mean subfoveal

Table IV: Comparison of choroidal thickness among studies

Author/year	Read et al. 2013[9]	Jin et al. 2016[13]	Lee et al. 2017[20]	Fontaine et al. 2017[22]	Qi et al. 2018[19]	Xiong et al. 2020[15]	Present study. 2025
Country	Australia	China	Korea	France	China	China	Malaysia
Age	10 – 15	7 – 13	6 – 12	2 – 16	8 – 11	6 – 16	7 – 17
Number of subjects	104	276	89	115	120	402	109
Myopia	41	86	28	35	120	402	88
Emmetropia	63	91	39	80			21
Hyperopia		99	22				
SFCT in myope (μm), Mean (SD)	303 (79)	227 (61)	267.46 (63.14)	268.55 (86.95)	252.80 (46.95)	294.16 (77.59)	284.91 (70.88)
SFCT in emmetrope (μm), Mean (SD)	359 (77)	253 (58)	301.97 (55.93)	328.85 (33.90)			347.62 (35.81)
Axial length in myope (mm), Mean (SD)	24.46 (1.07)	24.17 (0.96)	24.32 (0.70)	24.5	24.54 (0.79)	24.67 (0.93)	25.02 (1.73)
Axial length in emmetrope (mm), Mean (SD)	23.26 (0.64)	23.25 (0.72)	23.16 (0.77)	22.1			22.77 (0.60)

SFCT = subfoveal choroidal thickness, SD = standard deviation

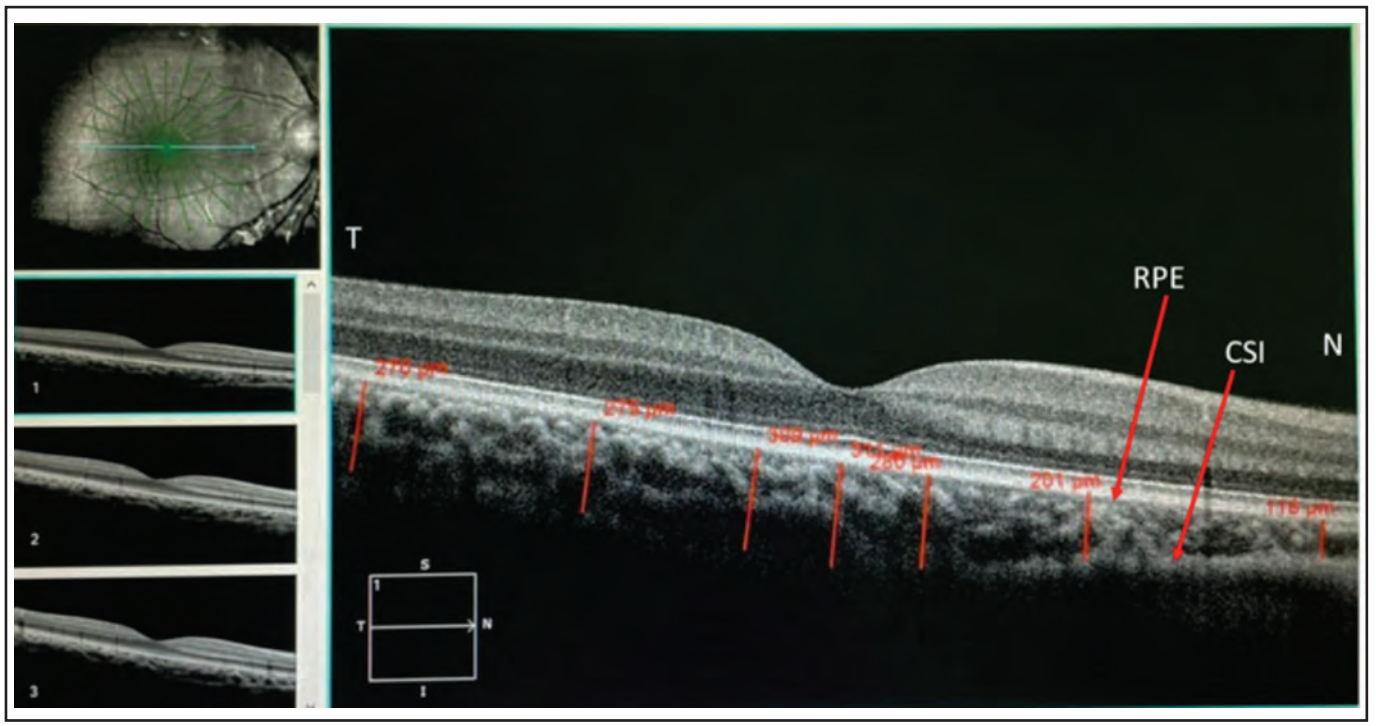

Fig. 1: Overview of OCT scanning protocol and analysis procedure used in the study. Each subject had 12 HD radial OCT scan line images captured centred on the fovea

choroidal thickness was 294.[16] (77.59) μm.[15] The mean subfoveal choroidal thickness in myopic Malay children in our study was consistent with the range of reported choroidal thickness among the Chinese myopic children as illustrated in Table IV (227.00 (62.00) to 294.16 (77.59) μm).[13,15,17] Our findings agree with other myopic adult and children studies that myopia has been associated with thinner choroid.[9,14,15,18] It is hypothesized that rapid axial elongation before myopia onset causes choroidal layer thinning leading to decreased choroidal blood flow and subsequently scleral ischaemia and hypoxia, as well as scleral thinning and weakening, which would lead to excessive axial elongation and development of myopia.[9]

Our population showed significant differences in choroidal thickness among different degrees of refractive error. We found that the high myopia group has marked thinning of the choroidal layer compared to mild and moderate myopia groups. The difference in mean choroidal thickness between the moderate and high myopia group was twice greater than the difference between the moderate and mild myopia group. This finding was similar to other studies in China, Indonesia, Egypt and Spain.[19-22] Populations with a high prevalence of myopia tended to have thinner choroid.[10,13,23] Accelerated growing eyeball due to myopia leads to choroidal vascular and connective tissue remodeling resulting in loss of choroidal volume and diminished blood supply.[9,16,24] This indicated that choroidal thinning is a feature observed in

myopia progression. Our observation is supported by histological study of the highly myopic eyes showed defect in the macula Bruch membrane with the absence of choriocapillaries except very few large choroidal vessels and almost complete absence of photoreceptors.[25] These findings could be due to excessive stretching of the posterior segment. Thus, the high myopia group is at very high risk of developing choroidal neovascularization resulting in poor visual function.

Our study observed the thickest choroid at the subfoveal zone in all degrees of refractive error. The choroids progressively thinner towards the periphery with the thinnest choroid observed at the nasal outer macula zone in both myopic and emmetropic eyes. Our findings were comparable with a study among myopic Australian children aged ten to fifteen where the choroidal layer was thickest in the central macula and thinnest nasally.[11] Studies of choroidal thickness in normal eyes without refractive error also found a topographic variation of choroidal thickness at the posterior pole with the thickest choroid at the subfoveal zone.[22] Few studies, meanwhile, have documented the thickest choroidal layer in the temporal zone of myopic children and adults.[13,17,20,26,27] This could be due to the elongation of the eyeball resulting in the shifting of the choroids temporally. However, we believe that growing choroids in children may not have the same pattern as adults, as observed in our populations.

We also found a greater difference between central and nasal macula choroidal thickness between eyes with high myopia and mild myopia compared to differences in more temporal locations. This showed that the degree of choroidal thinning from centre to the peripheral nasal macula was greater in high myopic eyes. The thin nasal choroidal layer observed in many studies is also associated with the severity of myopic maculopathy which can be a devastating myopia complication.[20]

Many studies concluded that choroidal thickness increases in growing children without refractive error until it reaches a peak in adolescence.[9,27,28] However, our study found no significant correlation between age and choroidal thickness, similar to a study done in Daegu, Korea involving children aged six to twelve years.[18] On the contrary, studies done in Shanghai, China found a decrease in choroidal thickness with age.[13,14] However, their studies involved younger children aged six to nine. It was reported that there was a negative correlation between choroidal thickness and age in Asian children which could be due to the very high prevalence of myopia in their population but a positive correlation was noted among white children.[29] We postulated that changes in choroidal thickness with myopia development in our study population could not be due to passive stretching alone. The high metabolic demand of the growing eyes could explain the increase in choroidal thickness with age.[27] Thus, our study observed the presence of balance between changes in choroidal thickness due to ocular growth and axial elongation contributing to myopia development.

A positive correlation between choroidal thickness and spherical equivalence has been well established in previous adult and child studies.[9,14,28,30] We observed that the choroidal layer became progressively thinner in myopia as the spherical equivalent became more negative. Our findings consistent with experimental myopia induced in animal studies showed rapid thinning of choroid followed by an increase in eye growth.[31] Visual deprivation and the addition of a plus lens which makes the animal eyes myopic caused modulation of the choroidal layer in order to bring the image to focus on the retina.[31] Thus, optical factors such as chronic hyperopic defocus associated with a lag of accommodation during near tasks could contribute to thinner choroid in myopic children.

We reported a significant negative correlation between choroidal thickness and axial length. Our findings agree with most previous studies that a significant negative correlation exists between axial length and choroidal thickness.[5,26] A large myopia study in China found that the rate of change in refraction and axial elongation accelerated before the onset of myopia and slowed gradually after myopia was established.[32] A study done in two to 16 years old France children showed thinning of subfoveal choroid with myopia progression and an increase in subfoveal choroidal thickness in nonmyopic children.[20] Axial length increases rapidly in early childhood as the child grows. It is possible that due to growing eyeball causes passive stretching of the outer coats of the eyeball which leads to thinner choroid. However, the degree of choroidal thinning could be higher than the thinning predicted based on a passive stretch of the choroid from the axial elongation of myopia.[9]

The first limitation of our study is the cross-sectional design did not allow us to attribute causation to the association between choroidal thinning to myopia onset and progression. Individual variations in choroidal thickness are common, and choroidal thickness alone may not fully explain the complexities of myopia development in children. Choroidal thinning in our myopic children may not be the consequence of myopia but rather its onset of development and progression. We suggest that a longitudinal study to monitor choroidal thickness alongside other parameters may provide a more comprehensive understanding of myopia progression and its potential impact on ocular health.

Cycloplegic agents such as tropicamide, phenylephrine and cyclopentolate 1% cause significant decrease in the subvofeal choroidal thickness.[33,34] Use of anti-muscarinic agent such as atropine caused significant increase in the choroidal layer of healthy children even without significant change in axial length.[35] Thus, non-cycloplegic refraction was preferred to avoid confounding effect of cycloplegic agents on the choroidal layer. However, lack of cycloplegia may influence reliability of refraction in children thus, a limitation in our study. Another limitation of the present study is that the measurement of the choroidal thickness was performed manually. However, other studies done in adults and children with myopia using Cirrus OCT with manual measurement of the choroidal layer produce high reliability and reproducibility.[14-16,36] Automated software will be required for more objective evaluation.

CONCLUSION

This study found new data on variations of choroidal thickness among myopic and emmetropic Malay children. The choroidal layer in myopic Malay children was thinner than in the emmetropic group with the greatest thinning observed in the high myopia group. The thinning of the choroidal layer occurs with the worsening severity of myopia and the increase in axial length. The increasing prevalence of high myopia in our population is alarming and warrants early detection of myopia development and control. Thus, myopic children need regular and close follow-ups for axial length, choroidal imaging and various strategies to control myopia progression.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE

Impact of computerized provider order entry system on medication prescribing errors in hospital wards: a comparative study

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ABSTRACT

Introduction: Medication errors are a major concern in healthcare, threatening patient safety and increasing costs. These errors can occur at various stages, from prescribing to dispensing and administration. Among these, prescribing errors are particularly critical as they occur at the initial step of medication use process and can propagate downstream, potentially leading to adverse events. Computerized provider order entry (CPOE) systems, with integrated clinical decision support tools offer significant benefits over handwritten prescriptions including enhanced legibility, prescription completeness, standardization, a comprehensive audit trail and real-time alerts and reminders to assist prescribers during the prescribing process. This study aims to evaluate the effectiveness of a CPOE system with clinical decision support features in reducing prescribing errors across the hospital. It compares the rates and error types between electronic and handwritten prescriptions over different time periods following the CPOE implementation.

Materials and Methods: This retrospective comparative analysis examines inpatient prescription data collected from the same hospital wards during three distinct periods: 1st January to 31st March 2023 (59,663 handwritten prescriptions), 1st October to 31st December 2023 (43,363 electronic prescriptions at 3 months post-CPOE implementation) and 1st January to 31st March 2024 (44,317 electronic prescriptions at 6 months post-CPOE implementation). The CPOE system was implemented in July 2023.

Results: The CPOE system significantly reduced medication prescribing errors (3 months post-CPOE: n=832, 1.92%; 6 months post-CPOE: n=617, 1.39%) compared to handwritten prescriptions (n=3532, 5.92%). The odds of errors occurring 3 months and 6 months post-CPOE implementation were 65% and 75% lower, respectively, than during the handwritten phase [Odds Ratio (OR), 0.35; 95% Confidence Interval (CI), 0.32 - 0.38] and [OR, 0.25; 95% CI, 0.23 - 0.28]. Potential error sources associated with handwritten prescriptions, such as illegible prescriptions, non-standard abbreviations and incomplete prescriptions, were entirely eliminated with CPOE adoption. Significant differences in error types were observed between handwritten and electronic prescriptions (p<0.001). However, errors related to incorrect dosage, frequency and unit of measurement increased under the CPOE system compared to handwritten prescriptions (p<0.001). A significant reduction in odds occurred with wrong unit of measurement [OR, 0.61; 95% CI, 0.52 - 0.72) followed by frequency errors [OR, 0.58; 95% CI, 0.47 - 0.73) from the 3 months to 6 months post-CPOE implementation. Non-significant reductions or increments in odds were observed for other error types including wrong dosage, wrong route, wrong form, wrong strength and wrong or inappropriate drugs between the two 3-month post-CPOE periods.

Conclusion: The implementation of the CPOE system has significantly minimized the factors contributing to medication prescribing errors associated with handwritten prescriptions. However, the CPOE-related errors can still occur and may persist or change over time. To further improve prescribing safety, it is essential to address the factors contributing to these errors and periodically assess them to minimize the gap. Future studies should explore additional aspects of medication safety such as prescriber knowledge, types of medicines prescribed, long term error patterns and contextual factors including disease complexity across clinical settings, particularly with the integration of advanced clinical decision support tools.

KEYWORDS:
Computerized provider order entry (CPOE) systems, medication errors, handwritten prescription, prescribing errors, clinical decision support

INTRODUCTION

Medication errors represent a significant challenge in healthcare, posing risks of patient harm and increased costs.[1,2] These errors encompass prescribing the wrong medication, administering incorrect doses, omitting vital drugs, failing to recognize drug interactions or allergies. They can occur at various stages of the medication use process, from prescription to dispensing and administration, and may result from factors such as illegible handwriting, personal circumstances (e.g., fatigue), environmental context (e.g. interruptions or heavy workload), or lack of knowledge.[3,4]

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To address these challenges, computerized provider order entry (CPOE) systems offer a promising solution to reduce medication errors and enhance patient safety.[5-7] CPOE systems allow healthcare providers to electronically enter and manage medication orders, replacing traditional paper-based methods. By standardizing order entry, CPOE improves legibility and reduces the likelihood of misinterpretation or transcription errors, which is a key advantage of these systems. Additionally, the integration of clinical decision support (CDS) tools into CPOE systems provides real-time alerts and reminders, preventing errors such as drug interactions, allergies, or incorrect dosages.[8-11] These tools also promote evidence-based treatments, enhancing both patient outcomes and care efficiency.[8-11]

CPOE implementation has been recognized as a benchmark for improving patient safety by organizations such as the Leapfrog Group, the Agency for Healthcare Research and Quality, and the Institute of Medicine.[12-14] Globally, CPOE systems are increasingly adopted to mitigate issues like illegible handwriting, incomplete orders, and transcription errors.[15-18] However, despite their effectiveness, CPOE systems can also introduce unintended consequences, such as wrong patient orders, duplicate orders, or incorrect order selection.[16,19,20] These unintended outcomes underscore the importance of considering both the advantages and disadvantages of CPOE implementation. Recognizing these risks is essential for developing targeted implementation strategies to maximize safety and efficiency in clinical practice.

Although CPOE systems are computer applications capable of managing orders for medications, laboratory tests, radiology, referrals, and procedures, this study focuses exclusively on their use for the electronic entry of medication orders. Among the medication errors, prescribing errors are particularly critical as they occur at the initial step of medication use process and can propagate downstream, potentially leading to adverse events. By narrowing the scope to medication prescribing errors, a significant subset of medication errors, this study provides detailed insights into how CPOE impacts prescribing rates and type. Dispensing and administration errors are excluded, ensuring a focused evaluation of prescribing errors. To systematically assess the impact of CPOE implementation, a predefined list of prescribing error types, including dose, frequency, and strength errors, was developed prior to the study. This structured approach ensures consistency in analysing error trends.

By comparing rates and types of medication prescribing errors between electronic and handwritten prescriptions across different time periods following CPOE implementation, this study aims to enhance understanding of both the risks and benefits associated with the system. Ultimately, the goal is to enhance patient safety, improve care quality and deliver greater value in clinical practice

MATERIALS AND METHODS

Study design

A before and after observational study was designed to evaluate medication prescribing errors by comparing the rate and types of errors that occurred before (handwritten) and after CPOE system implementation (electronically prescribed) over different time periods. The medication prescribing errors were extracted in two phases:

1) Phase 1 (Handwritten Prescriptions)
   During this phase, historical medication prescribing error data for handwritten prescriptions were collected from 1st January 2023 to 31st March 2023. Medication prescribing errors for this phase were extracted from handwritten prescriptions, including those intervened by pharmacy staff, with the information recorded on the prescriptions itself.

2) Phase 2 (Electronic Prescriptions)
   Two 3-month periods of electronic prescriptions with errors were extracted from the interventions conducted by pharmacy staff, with this information recorded in the Hospital Information System (HIS):

i) the first 3 months post-implementation (1st October 2023 to 31st December 2023)
ii) the second 3 months post-implementation (1st January 2024 to 31st March 2024).

Ethical approval was granted by Regency Specialist Hospital Ethics Committee. Waiver of consent was obtained as medical records were reviewed retrospectively.

Setting and population

The study took place in a 218-bed private hospital with 50,000 inpatients days annually, located in Masai, Johor, Malaysia. The hospital offers a comprehensive range of specialized healthcare services and comprises a total of 10 wards.

Prior to the implementation of the CPOE system in July 2023, all wards relied on paper medication charts for prescribers' handwritten orders. These charts underwent screening and verification by the pharmacy department before medications were dispensed to the wards. Prescribers were contacted for clarification as needed, and prescriptions were filled once errors were resolved. Intervened prescriptions were recorded directly on the prescriptions itself.

The HIS allows electronic prescribing whereby prescribers can enter prescription orders electronically into the HIS. Prescribers can select medications from pharmacy formulary or pre-selected favourite list. Subsequently, prescribers to select unit of measurement, frequency and duration. These fields are mandatory for prescription validation, as the system requires them to be filled before proceeding to the next order. All orders undergo thorough screening and verification by the pharmacy department. When an intervention is required, prescriber is contacted for confirmation and recorded in HIS. Medication preparation occurs once all details are confirmed to be correct.

The present analysis focused solely on prescriptions with errors, encompassing both handwritten and electronic prescriptions for the 6 months prior to, and 3 months and 6 months post-CPOE implementation. With this approach, we can evaluate changes in error rates and types between both types of prescriptions, as well as over time post-CPOE implementation. The data were de-identified or anonymized before analysis to protect the confidentiality of the patients and prescribers.

Table I: Characteristics of prescriptions with errors

Error Type	Pre-CPOE (Handwritten) (N=3083) n(%)	3-Month Post-CPOE (N=817) n(%)	6-Month Post-CPOE (N=606) n(%)
Legible handwriting[a]	2929(95.0)	817(100.0)	606(100.0)
Illegible handwriting[a]	154(5.0)	0(0.0)	0(0.0)
Without abbreviation[a]	2010(65.2)	817(100.0)	606(100.0)
Non-standard abbreviation[a]	1073(34.8)	0(0.0)	0(0.0)
Complete prescription[a]	855(27.7)	817(100.0)	606(100.0)
Incomplete prescription[a]	2228(72.3)	0(0.0)	0(0.0
Correct dosage[b]	3064(99.4)	606(74.2)	395(65.2)
Wrong dosage[b]	19(0.6)	211(25.8)	211(34.8)
Correct UOM[b]	3072(99.6)	443(54.2)	372(61.4)
Wrong UOM[b]	11(0.4)	374(45.8)	234(38.6)
Correct frequency[b]	3075(99.7)	595(72.8)	473(78.1)
Wrong frequency[b]	8(0.3)	222(27.2)	133(21.9)
Correct route[b]	3083(100.0)	804(98.4)	588(97.0)
Incorrect route[b]	0(0.0)	13(1.6)	18(3.0)
Correct form[b]	3059(99.2)	813(99.5)	596(98.3)
Wrong form[b]	24(0.8)	4(0.5)	10(1.7)
Correct strength[b]	3069(99.5)	814(99.6)	601(99.2)
Wrong strength[b]	14(0.5)	3(0.4)	5(0.8)
Correct drug[b]	3082(99.9)	816(99.9)	600(99.0)
Wrong/Inappropriate drug[b]	1(<0.1)	1(0.1)	6(1.0)

CPOE, computerized provider order entry; UOM, unit of measurement
[a] category A error
[b] category B error

Table II: Impact of computerized provider order entry (CPOE) on medication prescribing errors

	Handwritten	3-Month Post-CPOE	6-Month Post-CPOE	OR 95% CI	
				Handwritten and 3-Month Post-CPOE	Handwritten and 6-Month Post-CPOE
Total number of prescriptions reviewed	59663	43363	44317	-	-
Total number of prescriptions with one or more errors	3083	817	606	-	-
Total number of errors	3532	832	617		
Rate of medication prescribing error, %	5.92	1.92	1.39	0.35(0.32-0.38)*	0.25(0.23-0.28)*
Mean number of errors per prescription	1.14	1.02	1.02	-	-
Error type					
Wrong dosage[b]	19 (0.03)	211 (0.49)	211 (0.48)	15.34 (9.60 -24.54)*	15.02 (9.38-24.02)*
Wrong UOM[b]	11 (0.02)	374 (0.86)	234 (0.53)	47.18 (25.90-85.94)*	28.79 (15.72-52.70)*
Wrong frequency[b]	8 (0.01)	222 (0.51)	133 (0.30)	38.37 (18.95-77.69)*	22.45 (11.00-45.82)*
Other type errors[b]	39 (0.07)	21 (0.05)	39 (0.09)	0.74 (0.43-1.26)	1.35 (0.86-2.10)

CPOE, computerized provider order entry; CI, confidence interval; OR, odd ratios; UOM, unit of measurement
*p<0.001
[b] category B error

Table III: Impact of the computerized provider order entry (CPOE) system on medication prescribing errors with time, by error type

Error Type	3-Month Post-CPOE n (%)	6-Month Post-CPOE n (%)	p-value	OR 95% CI
Total Prescriptions	43363	44317		
Wrong dosage [b]	211 (0.49)	211 (0.48)	0.83	0.98 (0.81 to 1.18)
Wrong UOM [b]	374 (0.83)	234 (0.53)	<0.001	0.61 (0.52 to 0.72)*
Wrong frequency [b]	222 (0.51)	133 (0.30)	<0.001	0.58 (0.47 to 0.73)*
Wrong route [b]	13 (0.03)	18 (0.04)	0.41	1.35 (0.66 to 2.76)
Wrong form [b]	4 (0.01)	10 (0.02)	0.13	2.45 (0.77 to 7.80)
Wrong strength [b]	3 (<0.01)	5 (0.01)	0.53	2.45 (0.77 to 7.80)
Inappropriate drug [b]	1 (<0.01)	6 (0.01)	0.07	5.87 (0.71 to 48.77)

CPOE, computerized provider order entry; CI, confidence interval; OR, odd ratios; UOM, unit of measurement
*p<0.05
[b] category B error

Definition of terms
Medication error
A medication error refers to any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer.[21] These errors can occur at various stages, including prescribing, dispensing, administering or monitoring medications.

Some types of medication prescribing errors[15,22] identified in this study were as follow:

- Wrong/Inappropriate Drug: Prescribing a medication different from the intended one or indication or one which patient is allergic.
- Wrong Dosage: Prescribing an incorrect amount of medication, either too much or too little.
- Wrong Strength: Prescribing a medication with a strength different from the intended dosage.
- Incorrect Route: Prescribing a medication for administration through an incorrect method (e.g., oral instead of intravenous).
- Wrong Frequency: Prescribing the medication for administration at an incorrect timing.
- Wrong Dosage Form: Prescribing the incorrect physical form of the medication (e.g., tablet instead of liquid).
- Incorrect Unit of Measure: Prescribing the medication using an incorrect unit of measurement, leading to dosage miscalculations.
- Illegible Handwriting: Difficulties in interpreting the prescription due to unclear or illegible handwriting, potentially leading to errors in dispensing or administration.
- Incomplete Prescriptions: Occurring when essential information, such as dosage, frequency, instructions or patient details, is missing from the prescription, which can result in confusion or errors during medication administration.
- Non-Standard Abbreviations: Involving the use of abbreviations that are not standardized or understood universally, leading to misinterpretation and potential errors. This includes abbreviations specific to a particular healthcare discipline or facility, which may not be recognized by all healthcare professionals.

These medication prescribing errors fall under either category A (circumstances or events that have the capacity to cause error, e.g.; illegible handwriting, incomplete information or non-standard abbreviations) or category B (an error occurred but did not reach the patient), as categorised by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index, as they were detected during prescriptions screening.[21]

Study outcomes
The outcomes of interest were the rate and type of medication prescribing errors between handwritten prescriptions versus electronic prescriptions pre- and post-CPOE implementation.

Statistical analysis
Continuous variables were presented as mean and standard deviation while categorical variables were reported in frequencies and percentages. Error rates are expressed as errors per 100 prescriptions. A p-value of <0.05 was considered as statistically significant. Data were analysed using an online Confidence Interval calculator available at: https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/CI%20for%20ratio.htm

RESULTS

Prescription error characteristics are presented in Table I. Illegible, non-standard abbreviations, and incomplete prescriptions were prevalent during the handwritten phase but were completely eliminated with the adoption of the CPOE system. While some error types were observed in both handwritten and CPOE system, there was a notable increase in errors such as incorrect dosage, frequency, and unit of measurement under the CPOE system. Inappropriate drug errors, including drugs to which patients were allergic, were identified in the CPOE system both three and six months after its implementation.

The frequency of medication prescribing errors decreased from 5.92% to 1.92% after three months and further to 1.39%, six months post-CPOE implementation (Table II). The odds of an error occurring three months and six months post CPOE implementation were 65% and 75% lower, respectively, than during the handwritten phase [Odds Ratio (OR), 0.35; 95% Confidence Interval (CI), 0.32 - 0.38] and [OR, 0.25; 95% CI, 0.23 - 0.28]. The mean number of errors per prescription was found to be higher during the handwritten phase. Significant differences in error types and rates, particularly incorrect dosage, frequency, and unit of measurement under the CPOE system compared to handwritten prescriptions (p<0.001).

Table III summarizes the impact of the CPOE system on medication prescribing errors over time, categorized by error type. A significant reduction in odds was noted for wrong unit of measurement (39%) and wrong frequency errors (42%) post-CPOE implementation ($p<0.05$). Non-significant reductions or increments in odds were observed with wrong dosage, wrong route, wrong form, wrong strength, and wrong/inappropriate drugs between the two time-frames post-CPOE.

DISCUSSION

This study is among the few to evaluate medication prescribing errors following the implementation of CPOE with integrated basic CDS tools and to track their evolution over time in an inpatient hospital setting. Georgiou et al. reported that very few published studies have evaluated the real-world impact of CPOE systems, underscoring the importance of studies like ours that assess actual clinical outcomes in a working hospital environment.[23] Our findings showed a significant reduction in medication prescribing errors when comparing handwritten prescriptions to electronic prescriptions. The transition from handwritten to electronic prescriptions resulted in the complete elimination of issues such as illegible handwriting, non-standard abbreviations and incomplete prescriptions, which were prevalent during the handwritten phase. While certain errors, such as wrong unit of measurement and wrong frequency, initially increased after the introduction of the CPOE system, their rate dropped over time. However, dosage errors remained consistent throughout the post-CPOE period.

Given these findings, it is essential to consider the role of the integrated CDS tools in driving these improvements. While this study demonstrated a significant reduction in overall medication prescribing errors following the implementation of CPOE, the extent to which the CDS component contributed to this outcome warrants further examination. CDS tools provide real-time alerts and reminders, assisting prescribers in identifying potential drug interactions, incorrect dosages, and allergy-related contraindications. These features likely played a role in reducing specific types of prescribing errors[24] by providing timely feedback to the prescribers. This feature is particularly valuable in enhancing patient satisfaction and safety by allowing providers to correct errors immediately during order entry. The ability to correct errors at the moment of prescription will thereby enhance patient satisfaction with the implementation of CPOE. If the CPOE system had been implemented without CDS functionalities, the reduction in prescribing errors particularly those requiring clinical judgment would likely have been less pronounced. The standalone CPOE systems primarily mitigate errors related to legibility and completeness but may not effectively address more complex prescribing errors without integrated decision support.

Consistent to findings from other studies[5,16,18], our study revealed that the CPOE system has reduced medication prescribing error by at least 65% when comparing handwritten prescriptions to those electronic prescriptions. This reduction was particularly evident in errors classified as category A under the NCC MERP index[21], which includes legibility issues, missing information, and non-standard abbreviations. Category A errors can compromise prescription clarity and accuracy, potentially leading to confusion during preparation, dispensing, or administration. The adoption of CPOE systems significantly reduced these errors by enforcing standardized electronic ordering criteria, eliminating the need for abbreviations as all drugs are selectable from a drop-down menu. Additionally, CPOE ensures legible typing with standard sized fonts and formats that are easily readable and not prone to misinterpretation. Furthermore, the system includes built-in safety checks to ensure that prescriptions cannot proceed without all required information, further reducing the likelihood of missing information errors commonly seen in handwritten prescriptions.

Despite the significant reduction in overall prescribing errors, our study highlighted important shifts in error patterns, particularly regarding dosage, unit of measurement, and frequency errors. Unlike category A errors, which were effectively mitigated by the system, these specific errors showed a marked increase, with their rate rising from 0–5% in handwritten prescriptions to 20–45% in the post-CPOE phase. Notably, these errors were intercepted during pharmacist screening before reaching the patient, classifying them as category B errors. This pattern differed from that of category A errors. A key contributor to this increase appears to be selection errors associated with drop-down lists, a well-documented concern in other studies.[16,19,25,26] These errors occur when prescribers mistakenly choose the wrong option from a prepopulated list, resulting in unintended medication orders or incorrect dosing regimens. Another contributing factor include auto-populated information functionality of the system. When prescribers enter the first few letters or numbers of a drug name or dosage, the system suggests prefilled options that can be mistakenly selected.[27] Importantly, both the handwritten and CPOE prescriptions in this study were issued by the same team of specialists, yet selection errors were much lower in the handwritten prescriptions. This highlights the role of system design in contributing to these errors. Another possibility for the observed differences in error patterns was the under-detection of errors during the handwritten prescription phase. Factors such as illegible handwriting, lack of standardization, and incomplete documentation of pharmacist interventions could have led to missed or unrecorded errors. Some errors may have gone unnoticed due to time constraints, oversight, or variability in pharmacist expertise. Consequently, the apparent increase in dose and frequency errors during the CPOE phase may partly reflect improved error detection rates facilitated by electronic systems, rather than an actual rise in error occurrence. The structured data entry fields, enhanced traceability, and standardization of CPOE likely enabled more consistent error identification.

While improved detection may explain some of the observed increase, it is also crucial to acknowledge that CPOE implementation has introduced new challenges that require careful evaluation. Selection errors, particularly those associated with drop-down lists[16,19,25,26] and auto-populated fields[27], have been identified as major contributors to CPOE-related prescribing errors. Additionally, factors such as

prescriber knowledge gaps, contextual circumstances, fatigue, or inherent interface design flaws within the[3,4,28,29] may contribute to these errors. Alert fatigue, where frequent system notifications desensitize prescribers, can lead to oversight or dismissal of critical alerts.[8-11] Similaly, prescriber knowledge gaps, particularly regarding system functionalities and medication dosing, further increase the risk of CPOE-related errors.[3,4,28,29] Workflow misalignment, where system prompts do not align with clinical practices, can also impact prescribing accuracy.[3,4,28,29] To ensure continuous improvement, it is essential to periodically assess these factors, refine CPOE functionalities, and implement targeted interventions, such as enhanced clinical decision support tools and structured prescriber training. Our findings underscore the dual nature of CPOE's impact where it effectively eliminates preventable handwriting-related errors, it also introduces new, technology-related challenges[16,19,20,25,26] that require targeted interventions. To maximize the benefits of CPOE and minimize unintended errors, ongoing system refinements, user training, and monitoring mechanisms are essential. Future efforts should focus on enhancing the adaptability of CPOE to evolving clinical workflows, refining decision-support features, and implementing safeguards against selection errors. By continuously optimizing CPOE functionalities and addressing emerging challenges, hospitals can ensure that such systems contribute meaningfully to medication safety and overall patient care.

Over time, our study observed a significant reduction of approximately 40% in specific selection errors following CPOE implementation. Notably, there was a further decline in certain error types when comparing the initial three months following CPOE implementation to the subsequent three months. Specifically, wrong unit of measurement and wrong frequency errors showed even greater reductions in the second three-month period, suggesting that as users became more familiar with the system, their proficiency helped mitigate selection and navigation errors. Additionally, continuous updates and enhancements to the system to address initial usability issues or user interface challenges may have contributed to this improvement, making the system more intuitive and user-friendly. Changes in types and rates of CPOE-related errors over time have also been reported in other studies.[30,31] However, it remains unclear whether the types and rate of CPOE-related errors that emerge immediately after implementation are the same as those that persist or evolve after years of system use. Further studies need to be carried out to address this gap and to better understand the long-term implications of CPOE on medication safety.

While our study found that the implementation of CPOE significantly reduced medication prescribing errors, it is important to recognize the effectiveness of CPOE on medication safety can vary depending on the clinical setting and specific system configuration, as shown in previous studies.[23,29] Factors such as workflow integration, system configuration and prescriber training are crucial in determining safety outcomes. The unintended consequences such as new types of errors due to overdependence on technology, increased physician workload and workflow issues[3,4,16,19,20,23,29] underscores the importance of considering these variables in CPOE implementation. Recognizing how these factors influence CPOE's real world impact on medication safety is essential to optimizing its effectiveness across different clinical settings.

This study possesses several strengths. Firstly, it was conducted in a real hospital setting, providing findings applicable to actual clinical practice. Secondly, it directly compared error rates before and after CPOE implementation, offering a clear assessment of its impact. Thirdly, it analysed data over time, revealing how error rates evolved over time following CPOE adoption. Lastly, it identified factors contributing to errors in CPOE system, highlighting areas for potential improvement. However, there are also limitations to consider. The generalizability of this study to other hospitals may be limited since it was conducted in a single centre. This limitation, is partially mitigated by the use of predefined list of prescribing error types which ensures consistency in the analysis of error trends. Future research should validate these findings in diverse healthcare settings. Additionally, the three-month duration for each study phase might not capture long-term trends or fully assess the sustainability of error reduction achieved through CPOE implementation. Moreover, the study's focus solely on prescribing errors restricts the evaluation's comprehensiveness, as it does not encompass other potential outcomes or aspects of medication safety. Further we were unable to account for potential confounding factors such as variations in the prescribers' levels of expertise or differences in the types of medications prescribed, disease complexity and unmeasured influences. As reported by Bourdeaux et al., these factors may have affected the observed prescription errors throughout the study period.[29] However, we recognise the limitation of retrospective data collection for handwritten prescriptions where some errors may not have been documented. A potential limitation of our study is that the results were not stratified by individual wards. Since the data were compiled collectively (compiled data from all 10 hospital wards), we were unable to compare prescribing error trends across different wards. Stratification could have provided additional insights into whether certain wards experienced greater improvements or encountered specific challenges following CPOE implementation. Future studies may consider a ward-level analysis to explore variations in prescribing errors and optimize CPOE implementation strategies based on ward-specific needs.

CONCLUSION

This study demonstrated a significant reduction in medication prescribing errors following the implementation of the CPOE system. It effectively eliminated issues related to illegible, inappropriate, and incomplete prescriptions. However, CPOE-related errors have varied over time, emphasizing the need for continuous monitoring. Integrated CPOE with CDS tools is essential for improving drug management quality and safety, reducing medication errors and enhancing patient safety. To sustain these improvements, it is crucial to identify and address the underlying factors contributing to CPOE-related errors and periodically assess them to minimize gaps. Future studies should explore additional dimensions of medication safety,

focusing on the long-term error patterns and the influence of contextual variables, including disease complexity. Such research could further refine our understanding of CPOE's impact across different clinical settings, especially with the integration of advanced CDS tools. This integration may offer new opportunities for enhancing patient safety and optimizing the medication prescribing process, ultimately leading to better health outcomes.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Frequency of computer vision syndromes among students during COVID-19 lockdown – a single school study in Malaysia

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ABSTRACT

Introduction: To determine the frequency of computer vision syndromes among students during COVID-19 lockdown in Malaysia.

Materials and Methods: This is a cross-sectional survey study. A total of 145 subjects studied in secondary school and pre-university programme were involved in this study. An exploratory survey questionnaire was used to assess the symptoms of computer vision syndromes encountered by the students and their electronic device usage behavior before and during fully remote learning started.

Results: Average time spent by students on outdoor activities reduced from one to two hours per day (40.7%) to less than an hour per day (56.6%) after fully remote learning. Average time spent on entertainment activities using electronic devices increased from one to two hours per day (38.6%) to four hours and above per day (40.0%) after fully remote learning. The majority of time spent on school assignments using electronic devices increased from one to two hours (44.8%) to three to four hours per day (33.8%) after fully remote learning. Increased frequency of students experienced eye pain (44.1%), eye fatigue (57.2%), headache (56.6%), eye itchiness (18.6%), glare (31.7%), dry eye (40.0%), blurry vision (31.7%) and double vision (7.6%) after fully remote learning began.

Conclusion: An observed increase frequency of computer vision syndrome was noted in relation to the reduction of time spent on outdoor activities and increased usage of electronic devices for entertainment activities and completing school assignment during COVID-19 lockdown in Malaysia.

KEYWORDS:
computer vision syndromes; digital eye strain; electronic device usage behaviour; high school students

INTRODUCTION

Computer usage has extended greatly into our daily live raise the controversy of high electronic device usage and increase in screen time.[1] A recent report released in April 2021 found that there are currently 5.18 billion active internet users across the world, accounting for more than 60% of the global population.[2] Some support the idea that smart devices ease the learning process and improve quality of life,[3,4] but the others have opposed opinions. For instance, long-time exposure to visual display terminals has adverse effects on ocular and visual health, including blurred vision, ocular discomfort, and dry eye.[5] These groups of symptoms caused by visual display terminals are known as Computer Vision Syndrome (CVS).[6] Computer vision syndromes is a group of symptoms related to prolonged work using visual display terminal.[7] Computer vision syndromes also include other symptoms such as eye pain, eye fatigue, glare, double vision, headache, and neck and shoulder pain.[8]

Since the mid-term of 2019, the world has been hit with COVID-19 virus. Aggressive government policies were implemented immediately to combat the deadly pandemic,[9] with strict measures taken on social interactions by closure of public areas and prohibition of outdoor activities.[10] COVID-19 pandemic greatly impacted the lifestyles, health and work habits of all individuals.[11] To prevent further impact on global economic development, people started to adapt to the new lifestyle and shift their majority activities to online platforms. For instance, online meetings, remote working, online classes, online extra-curriculum program, and online grocery shopping.[12,13] A study conducted to investigate the association between digital screen time and digital eye strain during COVID-19 pandemic. The study reported that in this research sample, there was a notable rise in prolonged digital device usage during periods of home isolation, coinciding with a noticeable increase in the occurrence of digital eye strain during curfew implementations.[14]

The prevalence of quarantine measures and school closures has had a profound impact on the daily lives of school children. One significant consequence is that there has been a noticeable increase in the amount of time spent using digital devices, coupled with a rise in activities that require close up visual engagement. In tandem to that, there has been a significant reduction in outdoor activities as the circumstances necessitated staying indoors. While the

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duration of school closures might have been temporary, the extended period of reliance on digital platforms has led to a notable shift in behaviour and habits amongst children. This shift has fostered a heightened level of familiarity and comfort with digital tools, which causes them to have escalating reliance on electronic devices, which has the potential to endure beyond the COVID-19 pandemic.[15] The potential outcome of this should not be disregarded as it may affect children's wellbeing and development. Therefore, this study aims to identify: (1) time spent on electronic devices and physical activities before and after fully remote learning began due to COVID-19 lockdown, and (2) self-reported symptoms of computer vision syndrome before and after fully remote learning began due to COVID-19 lockdown.

MATERIALS AND METHODS

A cross-sectional survey study was conducted at Alice Smith School, Kuala Lumpur, within June 2021. The inclusion criteria of participants are students at their secondary level and pre-university program were recruited for voluntary survey responses. Students who were not fluent in English were excluded from the study. The subjects were required to answer the exploratory 36-item survey questionnaire of computer vision syndromes (Appendix A), based on their experience on symptoms related to computer vision syndromes and their electronic device usage behaviour before they started fully remote learning (May 2021) and after they started fully remote learning (June 2021) since COVID-19 lockdown.

RESULTS

A total of 145 students aged between 12 to 20 years in their secondary level and pre-university program were included in this study. 53 (36.6%) among the subjects were male and 92 (63.4%) were female.

Time spent on activities before fully remote learning

According to the subject response, 52 (35.9%) spent less than an hour for outdoor activity, 59 (40.7%) spent one to two hours on outdoor activities per day, 28 (19.3%) spent three to four hours on outdoor activities per day, and six (4.1%) spent more than four hours on outdoor activities.

For entertainment purpose, 21 (14.5%) spent less than an hour using electronic devices per day in average, 56 (38.6%) subjects spent one to two hours on electronic devices, 45 (31%) subjects spent three to four hours on electronic devices, while 23 (14.9%) subjects spent more than four hours on electronic devices in average.

Time spent on online extracurricular activities such as online yoga, handcraft, and other hobbies were reported. Seventy-four (51.0%) of the subjects spent less than an hour using electronic devices for online extracurricular activities, followed by 59 (40.7%) subjects who spent one to two hours per day in average, ten (6.9%) subjects spent three to four hours per day, and two (1.4%) subjects spend more than four hours per day on online extracurricular activities.

Thirty-seven (25.5%) among the subjects reported that, they spent less than an hour per day on electronic devices to complete school assignments, while 65 (44.8%) subjects spent one to two hours on electronic devices for school assignments, 26 (17.9%) subjects spent three to four hours on electronic devices for school assignment, and 17 (11.8%) subjects spent four hours on electronic devices for school assignment.

Time spent on activities after fully remote learning

In average, 82 (56.6%) spent less than an hour for outdoor activity, 54 (37.2%) spent one to two hours on outdoor activities per day, 7 (4.8%) spent three to four hours on outdoor activities per day, and two (1.4%) spent more than four hours on outdoor activities.

Thirteen (9.0%) spent less than an hour using electronic devices per day for entertainment purpose, 24 (16.6%) subjects spent one to two hours on electronic devices, while 50 (34.5%) subjects spent three to four hours on electronic devices, and majority (n = 58, 40.0%) of the subjects spent more than four hours on electronic devices for entertainment activities.

Time spent on online extracurricular activities such as online yoga, handcraft, and other hobbies were reported. Seventy-one (49.0%) of the subjects spent less than an hour using electronic devices for online extracurricular activities, 60 (41.4%) subjects who spent one to two hours per day in average, 7 (4.8%) subjects spent three to four hours per day, and three (2.1%) subjects spend more than four hours per day on online extracurricular activities.

Twenty-two subjects (15.2%) reported that, they spent less than an hour per day on electronic devices to complete school assignments, while 39 (26.9%) subjects spent one to two hours on electronic devices for school assignments, followed by 49 (33.8%) subjects spent three to four hours on electronic devices for school assignment, and 35 (24.2%) subjects spent four hours on electronic devices for school assignment.

Break interval while using electronic devices

Before fully remote learning was implemented, 37 (25.5%) subjects take break from screen use for less than an hour on average, 54 (37.2%) subjects take break from screen every hour, 40 (27.6%) subjects take break every two to three hours, and 14 (9.7%) subjects take break after screen time of four hours and above. After fully remote learning began, 38 (25.5%) subjects take break from screen use for less than an hour in average, 43 (29.7%) subjects take break from screen every hour, 37 (25.5%) subjects take break every two to three hours, and 27 (18.6%) subjects take break after screen time of four hours and above.

Self-reported break interval during online classes was recorded. Thirty-nine (26.9%) students reported that, break was taken less than every hour in average, 48 (33.1%) students reported taking break from screen hourly, followed by 34 (23.4%) students reported break interval for every two to three hours, and 24 (16.6%) subjects reported break interval for every four hours and above. Figure 1 illustrates the break interval of students before fully remote learning, during fully remote learning, and during online classes.

Table I: Time spent by students for different activities (n = 145)

Time spent on activities	Before fully remote learning	After fully remote learning
Outdoor activities		
< 1 hour	52 (35.9%)	82 (56.6%)
1 – 2 hour(s)	59 (40.7%)	54 (37.2%)
3 – 4 hours	28 (19.3%)	7 (4.8%)
> 4 hours	6 (4.1%)	2 (1.4%)
Entertainment (using electronic devices)		
< 1 hour	21 (14.5%)	13 (9.0%)
1 – 2 hour(s)	55 (38.6%)	24 (16.5%)
3 – 4 hours	45 (31%)	50 (34.5%)
> 4 hours	23 (15.9%)	58 (40.0%)
Extracurricular activities (using electronic devices)		
< 1 hour	74 (51.0%)	71 (49.0%)
1 – 2 hour(s)	59 (40.7%)	60 (41.4%)
3 – 4 hours	10 (6.9%)	7 (4.8%)
> 4 hours	2 (1.4%)	3 (2.1%)
School assignment (using electronic devices)		
< 1 hour	37 (25.5%)	22 (15.2%)
1 – 2 hour(s)	65 (44.8%)	39 (26.9%)
3 – 4 hours	26 (17.9%)	49 (33.8%)
> 4 hours	17 (11.8%)	35 (24.2%)

Computer vision syndromes

The ocular symptoms experienced by the students were assessed. Before the school started fully remote learning, 52 (41.6%) out of 145 subjects reported eye pain, 73 (58.4%) subjects had eye fatigue, 66 (52.8%) subjects had headache, 20 (16%) subjects had eye itchiness, 33 (26.4%) subjects had glaring, 48 (38.4%) subjects had dry eye, 39 (31.2%) subjects had blurred vision, and 6 (4.8%) among the subjects had double vision.

After fully remote learning began, there were 64 (44.1%) of the students experienced eye pain, 83 (57.2%) students had eye fatigue, 82 (56.6%) students reported headache, 27 (18.6%) students had eye itchiness, 46 (31.7%) had glare, 58 (40.0%) students reported dry eye, 46 (31.7%) students had blurred vision, and 11 (7.6%) had double vision.

During online classes, 47 (32.4%) subjects reported eye pain, 77 (53.0%) subjects had eye fatigue, 66 (45.5%) subjects had headache, 23 (15.9%) subjects had eye itchiness, 33 (22.8%) subjects had glaring, 49 (33.8%) subjects had dry eye, 32 (22.1%) subjects had blurred vision, and three (2.1%) among the subjects had double vision.

Frequency computer vision syndrome

Before fully remote learning, the majority of the students (40.7%) spent one to two hours per day on outdoor activities, shifted to less than an hour per day (56.6%) during fully remote learning. The majority of time spent on entertainment using electronic devices before fully remote learning was one to two hours per day (38.6%), increased to four hours and above per day (40%) during fully remote learning. The majority of time spent on extracurricular activities using electronic devices remained at less than an hour before (51%) and during fully remote learning (49%). The majority of time spent on school assignments using electronic devices was one to two hours (44.8%) before fully remote learning, increased to three to four hours per day (33.8%) during fully remote learning. According to the survey response, majority of the students take break from screen hourly before (37.2%) and after fully remote learning (29.7%). During online classes, the majority of the students (33.1%) take break from screen hourly as well. Table I shows the frequency of students and their time spent on outdoor activities, time spent on electronic devices for entertainment purposes, extracurricular activities and school assignments, and frequency of screen break.

Frequency of students experiencing Computer Vision Syndromes increased after fully remote learning began. Computer Vision Syndromes during online classes were reported, frequency of students experienced eye fatigue, eye itchiness and dry eye slightly increased, while frequency of students experienced eye pain, blurred vision and double vision during the online class reduced compared to before fully remote learning. Other than that, the frequency of students experienced headache and glaring remained as before fully remote learning. Figure 2 illustrates the frequency of students experiencing eye pain, eye fatigue, headache, eye itchiness, glare, dry eye, blurry vision, and double vision before fully remote learning, after fully remote learning and during online classes.

DISCUSSION

Survey results indicated that, majority of the subjects were using electronic devices for purposes of entertainment more than online classes and other purposes. As a result, fully remote learning method and online classes had mild effect on increasing symptoms of computer vision syndromes among secondary level and pre-university students in Malaysia. Although online classes itself does not have direct

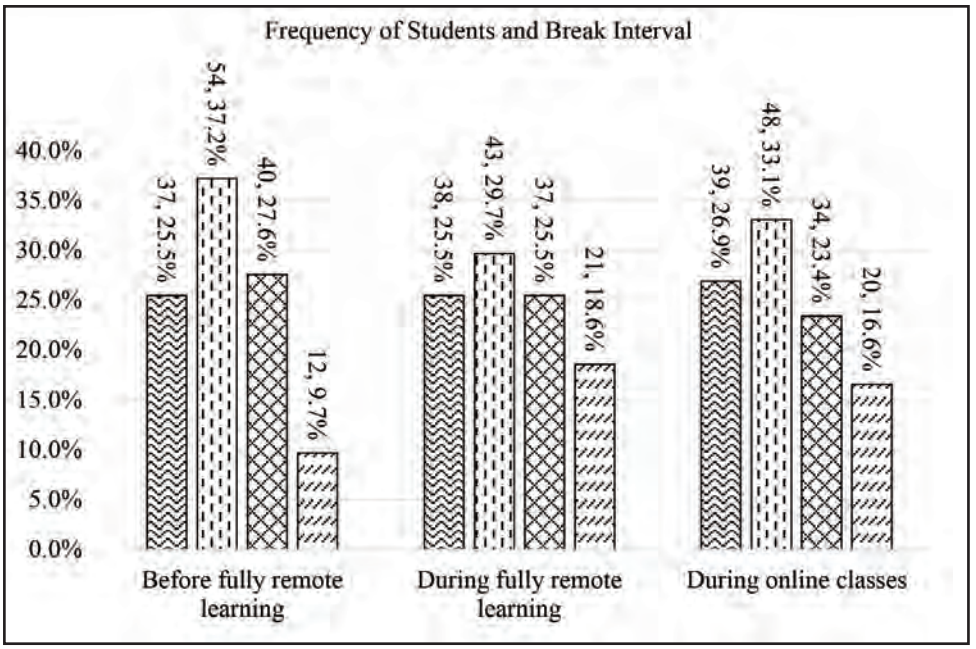

Fig. 1: Break interval during activities using electronic device

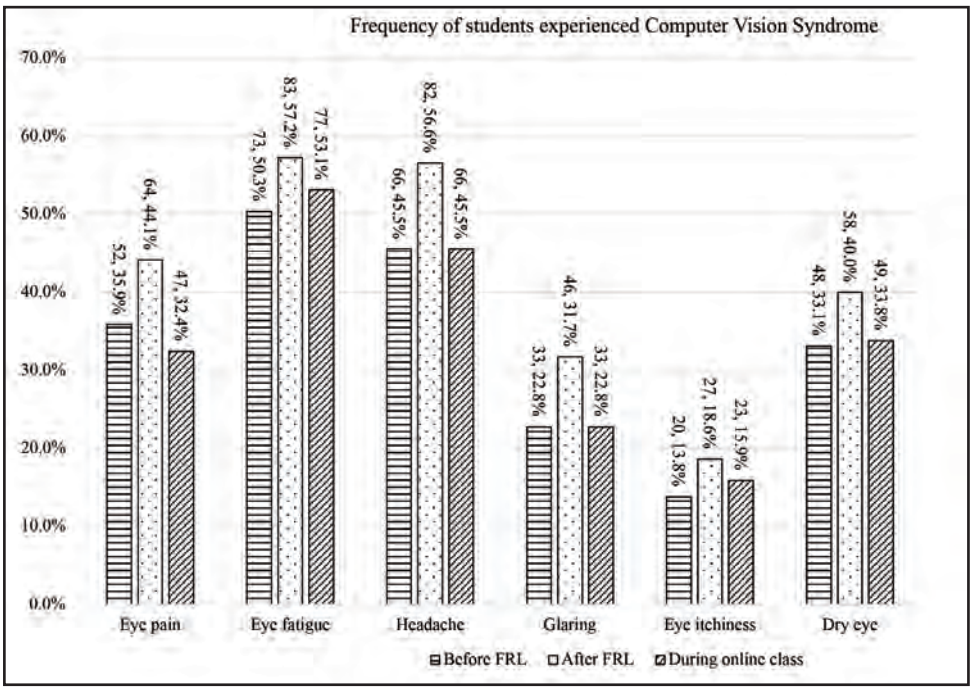

Fig. 2: Symptoms of CVS experienced by students in Malaysia (n = 145)

relation to computer vision syndrome, fully remote learning method due to strict movement control of residents resulted in a reduction for time spent of outdoor activities by the students, leading them to spend more time on electronic devices for entertainment and leisure with less self-limitation. Besides, the mode of school assignment has switched from hybrid (handwritten and digital assignment) to fully digital, which also leads to longer time spent on electronic devices.

Similar to this study findings, previous studies also reported that school-age children and young adults have increased internet usage during COVID-19 lockdown. A study done by Zandifar and Badrfam reported an increase in the access and usage of internet during COVID-19 lockdown. This is because COVID-19 pandemic has impacted various aspects of life, including the psychological well-being of populations, particularly among the young populations.[16] Previous studies reported an increase of stress, anxiety, and depression among the young populations during the pandemic.[17] By shifting to online education, young populations have relied heavily on digital platforms to keep in touch and connect with their friends and families.[18] Other than that, a study conducted amongst the young populations in Norway, examined the time spent on gaming and physical activities during COVID-

19 pandemic. The results showed that there was a notable increase in gaming activity during the initial COVID-19 lockdown in April 2020.[19] This hence points to the pandemic and its subsequent lockdowns had impact on the increase in digital engagement, not only for online classes, but also for other leisure activities.

Our study findings showed that there was an increase of students reported eye pain, eye fatigue, headache, glaring, eye itchiness, dry eye, blurred vision and double vision after fully remote learning began. This indicated that leisure activities using electronic devices impacted the ocular health and escalated computer vision syndrome among high school students in Malaysia. Similar study results were reported by previous studies. Bhattacharya et al.[20] studied on the computer vision syndrome among school-aged children in United Kingdom. The results reported 68% subjects had high usage of computers, and 54% among them started internet usage since the age of three, and the prevalence of computer vision syndrome was 69% among the adult subjects and 50% among the school-aged subjects.[20] Another study conducted in Lebanon has carried out a questionnaire among the working adults found that, subjects who transitioned to remote work had increased screen time and higher occurrence of experiences of computer vision syndrome. In which, these individuals were more susceptible to eye discomfort and eye strain due to prolonged usage of electronic devices.[21] Besides, a review to investigate the prevalence of computer vision syndrome during COVID-19 pandemic, reviewed subjects from 12 countries, resulting in 74% of subjects experienced computer vision syndrome during COVID-19 pandemic.[22]

According to the studied school and students, the average time for online classes was seven hours per day. Only symptoms of eye fatigue, dry eye and eye itchiness increased during online classes. This leads to an assumption where the increased of the symptoms might resulting from reduced blinking because the students were concentrating for learning. Earlier studies reported that, eye blink rate is significantly associated with level of attention, where blink rate reduced significantly with high attentive task.[23] Reduction of blink rate was a significant factor of evaporative dry eye associated with Meibomian gland dysfunction.[24,25] Other than that, implementation of online classes through virtual meetings significantly associated with eye fatigue experienced by students.[26] A study conducted by Kuwahara et al. reported that improper room lighting could lead to increase in eye fatigue.[27] However, there is a lack of published data on the standard or recommendation on the room lighting and screen lighting while using electronic devices for online classes and other activities.

The survey questionnaire used in this study was not validated due to time constraints for the study. However, the results may still psychometrically represent the targeted population in certain extent. One of the main limitations of this study is that the analysis was limited to descriptive statistics. This decision was based on concerns regarding the integrity and reliability of the data, as the questionnaire used was not subjected to validation or consistency tests, which might lead to biased outcomes and invalid interpretations. Therefore, future studies are needed urgently to address this limitation by employing validated and reliable tools, allowing for rigorous and statistical analyses that lead to a comprehensive and evidence-based conclusion. Besides, there is limitation due to the nature of self-reporting questionnaires, which there might be biases of the respondents according to their level of comprehension and psychological response. Furthermore, we acknowledge that recall bias may have affected the accuracy of reported symptoms and overgeneralizing the findings due to retrospective data collection resulting from the practical constraints during COVID-19 pandemic. In addition, the accuracy of the visual and ocular status has not been examined clinically, and the inter-rater reliability of the questionnaire items have not been studied. Therefore, the study results of the questionnaire might not be consistent or distorted, as there could be biases introduced among different questionnaire responders. Also, it is a single school study from an affluent area and may not represent the entire student population in Malaysia.

CONCLUSION

Reduction of time spent on outdoor activities, increased usage of electronic devices for entertainment activities and completing school assignments had an observed effect for computer vision syndrome after fully remote learning during COVID-19 lockdown. Therefore, it is advisable for the students to reduce time spent on unhealthy usage behaviour of electronic devices, especially on entertainment activities, and practice voluntary blinking exercise to reduce symptoms of dry eye and eye itchiness. The ministry of education and school authorities in Malaysia were aware of the break interval of students during online classes. However, eye care practitioners, school authorities and parents should work concurrently to raise awareness of the students about the impact of prolonged screen time to ocular and visual health. Besides, eye care practitioners need to understand the electronic usage behaviour of each patient for a better and effective management of computer vision syndromes.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Appendix A

Survey questionnaire of computer vision syndromes

The following questions consists of **THREE SECTIONS,** please answer the questions in **SECTION A** based on your experience within **previous month (before fully remote learning)**, answer questions in **SECTION B** based on your experience within **this month (during the fully remote learning)**, and answer questions in **SECTION C** based on your experience **during online classes**.

Date

Name: **Age:** **Gender:** ☐ Male ☐ Female

SECTION A: BEFORE FULLY REMOTE LEARNING
Answer the following questions based on your experience within previous month: -

1. How many hours, on average did you spend for outdoor activities in a day?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

2. On average, how many hours a day did you spend on entertainment using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

3. On average, how many hours a day did you spend on completing school assignment using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

4. On average, how many hours a day did you spend on extracurricular reading using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

5. On average, how frequent did you take breaks from your electronic device(s)?
   ☐ Less than every hour
   ☐ Every hour
   ☐ Every 2 to 3 hours
   ☐ Every 4 hours and above

6. Did you experienced eye pain after using electronic device(s)?
   ☐ Yes
   ☐ No

7. Did you experienced eye fatigue after using electronic device(s)?
   ☐ Yes
   ☐ No

8. Did you experienced headache after using electronic device(s)?
   ☐ Yes
   ☐ No

9. Did you experienced glaring after using electronic device(s)?
   ☐ Yes
   ☐ No

10. Did you experienced itchiness of eye after using electronic device(s)?
   ☐ Yes
   ☐ No

11. Did you experienced dry eye after using electronic device(s)?
   ☐ Yes
   ☐ No

12. Did you experienced blurred vision after using electronic device(s)?
   ☐ Yes
   ☐ No

13. Did you experienced double vision after using electronic device(s)?
   ☐ Yes
   ☐ No

SECTION B: AFTER FULLY REMOTE LEARNING
Answer the following questions based on your experience within this month: -

14. How many hours, on average did you spend for outdoor activities in a day?
   ☐ Less than 1 hour
   ☐ 1 to 2 hour(s)
   ☐ 2 to 4 hours
   ☐ More than 4 hours

15. What type of electronic device(s) did you use?
   ☐ None
   ☐ Smartphone
   ☐ Tablet
   ☐ Laptop
   ☐ Desktop

16. On average, how many hours a day did you spend on entertainment using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

17. On average, how many hours a day did you spend on completing school assignment using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

18. On average, how many hours a day did you spend on extracurricular reading using electronic device(s)?
   ☐ Less than 1 hour
   ☐ 1 to 2 hours
   ☐ 3 to 4 hours
   ☐ More than 4 hours

19. On average, how frequent did you take breaks from your electronic device(s)?
    - ☐ Less than every hour
    - ☐ Every hour
    - ☐ Every 2 to 3 hours
    - ☐ Every 4 hours and above

20. Did you experienced eye pain after using electronic device(s)?
    - ☐ Yes
    - ☐ No

21. Did you experienced eye fatigue after using electronic device(s)?
    - ☐ Yes
    - ☐ No

22. Did you experienced headache after using electronic device(s)?
    - ☐ Yes
    - ☐ No

23. Did you experienced glaring after using electronic device(s)?
    - ☐ Yes
    - ☐ No

24. Did you experienced itchiness of eye after using electronic device(s)?
    - ☐ Yes
    - ☐ No

25. Did you experienced dry eye after using electronic device(s)?
    - ☐ Yes
    - ☐ No

26. Did you experienced blurred vision after using electronic device(s)?
    - ☐ Yes
    - ☐ No

27. Did you experienced double vision after using electronic device(s)?
    - ☐ Yes
    - ☐ No

SECTION C: DURING ONLINE CLASSES

Answer the following questions based on your experience during online classes: -

28. How frequent did you take breaks from your device(s) during online classes?
    - ☐ Less than every hour
    - ☐ Every hour
    - ☐ Every 2 to 3 hours
    - ☐ Every 4 hours and above

29. Did you experienced eye pain after using electronic device(s)?
    - ☐ Yes
    - ☐ No

30. Did you experienced eye fatigue after using electronic device(s)?
    - ☐ Yes
    - ☐ No

31. Did you experienced headache after using electronic device(s)?
    ☐ Yes
    ☐ No

32. Did you experienced glaring after using electronic device(s)?
    ☐ Yes
    ☐ No

33. Did you experienced itchiness of eye after using electronic device(s)?
    ☐ Yes
    ☐ No

34. Did you experienced dry eye after using electronic device(s)?
    ☐ Yes
    ☐ No

35. Did you experienced blurred vision after using electronic device(s)?
    ☐ Yes
    ☐ No

36. Did you experienced double vision after using electronic device(s)?
    ☐ Yes
    ☐ No

Uterine torsion in pregnancy: a case report and systematic review

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ABSTRACT

Introduction: Uterine torsion in pregnancy is a rare condition but is associated with significant negative outcomes to the pregnant women and their babies. This study is to systematically review the literatures and analyse the clinical presentations, management and complications of uterine torsion in pregnancy.

Materials and Methods: We searched across multiple databases (PubMed, Google Scholar, ScienceDirect, Academia.edu, ResearchGate and Semantic Scholar) and suitable articles from 1993 to 2022 were systematically chosen according to PRISMA guideline. The analysis was performed on the maternal characteristics, signs and symptoms of the uterine torsion, management, complications and outcomes of both the mothers and infants. All case reports or case series reporting uterine torsion in pregnancy from English language journals were included without restriction on the geographical origin.

Results: A total of 149 cases from 146 publications and one from our centre were included for analysis. Most of the cases were seen in the third trimester and presented with acute abdominal symptoms and signs. It presented a challenge in diagnosis and had a myriad of complications to the mothers and infants. The maternal mortality is 2.0% while the perinatal mortality stands at 38.2%.

Conclusion: Uterine torsion in pregnancy is a rarely encountered but serious condition with no specific precipitating factor or diagnostic criteria. It can occur at any gestation, has a wide range of non-specific clinical presentations, and carries a significant risk to the mother and child.

KEYWORDS:
uterine torsion, pregnancy, systematic review

INTRODUCTION

Uterine torsion is a relatively rare condition in humans but commonly encountered in animals, with the bulk of literature being about ungulates such as buffalo, cow, horse and ewe. It had also been reported in smaller animals such as dogs, rabbits and guinea pigs which is explained by the quadruped posture of these animals that allows the uterus to be mobile.[1] The pathology was first described in 1662 by a veterinary surgeon, Hippiaper Columbi, and in humans, the first description was from a postmortem examination by Rudolf Virchow in 1863. In pregnancy, uterine torsion was first reported by Labbe in 1876.[2]

Previously, the terminology torsion was used in cases where the uterine displacement is associated with signs and symptom.[3] Later reports showed that not all torsion has symptoms or signs, hence the alternative definition was chosen. Nowosielski & Henderson suggested that the diagnosis of torsion should be considered when the axial rotation exceeds 30°.[4] Currently, the most accepted definition is that the rotation is 45° or more at the longitudinal axis.[5]

There are several reviews on uterine torsion in pregnancy and one of the largest is by Jensen in 1992, discussing the findings from 212 cases.[6] Since then, there have been one systematic and two literature reviews but the number of publications included were limited due to their restrictive search criteria.[7-9] Here, we present a case managed at our centre and a systematic review of this rare entity with an expansive search across multiple literature databases.

CASE REPORT

A 30-year-old pregnant woman, gravida 3 and parity 2, presented at 36 weeks of gestation with sudden onset abdominal pain, associated with vomiting started five hours earlier. She also reported a reduction in fetal movement, but no vaginal bleeding or fluid loss and was not in labour. Previous pregnancies were uncomplicated, as was the index pregnancy before this acute event. Her vital signs were stable, and the uterus was soft, non-tender and the size corresponded to the gestation. Ultrasound examination showed a single fetus in transverse lie with no fetal heart activity, and placenta was on the anterior uterine wall with an estimated 128 mL of blood clot seen at the placental edge. There was no uterine contraction, nor any cervical changes and all blood investigations were within the normal range. The patient was explained about the intrauterine fetal death with signs of placental abruption and was offered caesarean section as the fetus was in transverse lie.

The surgery was performed under spinal anaesthesia via a transverse suprapubic incision. Large, dilated vessels were seen transversing the lower uterine segment and the vesicouterine fold could not be located. Further examination revealed a 180°, clockwise uterine torsion with an engorged left fallopian tube and ovary located on the right side. Manual internal and external manipulation successfully reverted the torsion, and the fetus was delivered via breech

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extraction through a lower segment transverse hysterotomy as per usual caesarean section. There was a brief episode of uterine atony that responded to intramuscular prostaglandin and oxytocin infusion. The total estimated blood loss was 600 mL with half of it from the abruptio placentae.

The patient had a full recovery before going home two days after the surgery. She was seen again six weeks later where an ultrasound examination, including Doppler study of the uterine vessels, showing normal pelvic anatomy. The antenatal record reviewed before the patient was discharged showed that the placenta was observed on the posterior wall during a midtrimester ultrasound, a sign highly suggestive of uterine torsion but was not realized before the delivery.

MATERIALS AND METHODS

A protocol with explicitly defined objectives, criteria for study selection, search criteria, and statistical methods was developed. We followed the reporting guidelines for meta-analyses and systematic reviews, as outlined by the PRISMA statement.[10]

The primary objective was to investigate the outcomes of uterine torsion in pregnancy, the maternal and perinatal mortality. Other related data such maternal characteristics, presenting signs and symptoms, related surgical procedures, possible precipitating factors, maternal and perinatal morbidity were also extracted and analysed.

Data source and search strategies

The initial search was performed for indexed articles in PubMed. This was later expanded to include other publications in Google Scholar, ScienceDirect, Academia.edu, ResearchGate and Semantic Scholar. The terms used for the search were "uterine torsion", "uterus" AND "torsion" with and without "pregnancy".

A full title and abstract screening were performed independently by two reviewers. Reference lists of the articles collected were later searched for additional relevant articles for inclusion. A full-text screening was then independently undertaken by these reviewers to determine relevance and the final set of articles was reviewed in detail before the data elements were extracted for analysis.

Eligibility and study selection

All case reports or case series, short communications and research letters describing uterine torsion during pregnancy between 1993 and 2022 were included. This time frame was chosen as one of the largest reviews on this pathology was published in 1992, but it included reports from 1800s which discussed cases that had undergone management that are no longer practiced today. There was no limitation on the geographical origin of the publications, but only English language full text articles were chosen for final analyses. We excluded uterine torsion outside the pregnancy including the postpartum period.

Data collection

Articles selected for inclusion were carefully reviewed by the authors, and appropriate data were extracted. Variables included were the parity and gestational age at diagnosis, signs and symptoms related to the torsion, especially abdominal pain, tenderness, rigidity and shock. The surgical techniques were also recorded, such as the type of laparotomy (or laparoscopy), location (anterior or posterior; lower segment or upper segment) and type of hysterotomy (transverse or longitudinal). Also of interest were the other surgeries performed such as hysterectomy, resection of the rudimentary uterine horn, myomectomy and ligaments plication. The timing of diagnosis (before or after the hysterotomy), the detorsion attempt and degree of torsion were also analysed. Associated findings such as the fetal lie at presentation, Müllerian tube abnormality, fibromyomata or adhesion were included in the data collection. Data extraction was finally concluded with maternal and perinatal outcomes.

Risk of bias assessment

The risk of bias was assessed independently by two reviewers, using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series.[11] Any discrepancy was resolved by discussion and reassessment.

Statistical analysis

Data for categorical variables were directly extracted and presented as numbers and percentages while mean or median, and median interval were calculated for continuous data. Perinatal mortality rate was calculated from pregnancies that had completed 22 weeks of gestation.[12] Data handling and analysis were performed using Statistical Package for Social Science (SPSS) version 27 (SPSS Inc, Chicago, IL, USA) software.

RESULTS

The initial search identified 79 full text articles from PubMed with additional 124 articles from Google Scholar, 89 from Semantic Scholar, 75 from ResearchGate, 19 from Academia.edu, 14 articles from ScienceDirect with 4 additional articles identified from citation tracking. After excluding duplicated papers, non-English and non-retrievable articles, a total of 146 were selected (Fig.1). These publications discussed 149 cases and with a case described from our centre, a total of 150 cases of uterine torsion in pregnancy were included in this review. This search strategy identified 85 publications not included in previous reviews.[13-97]

Risk of bias of the included studies

Overall, the risk of bias, assessed using JBI critical appraisal tool was judged to be low for the description of patient demographic characteristics, history and clinical presentations, diagnostic procedures, and treatment in all cases. Only one case had unclear patient's demographic. Unanticipated events or complications and takeaway lessons were also judged to be of low bias risk except for in three articles. The post-intervention clinical condition: the fetal or neonatal outcome was not available in six cases and was uncertain in one article (Appendix 1).

Uterine torsion characteristics, diagnosis and management

The mean age of the women involved was 30.4 years (range 16 to 43) while the mean gestation at diagnosis was 33.7 weeks (range 7 to 41 weeks). The majority were in the 3rd

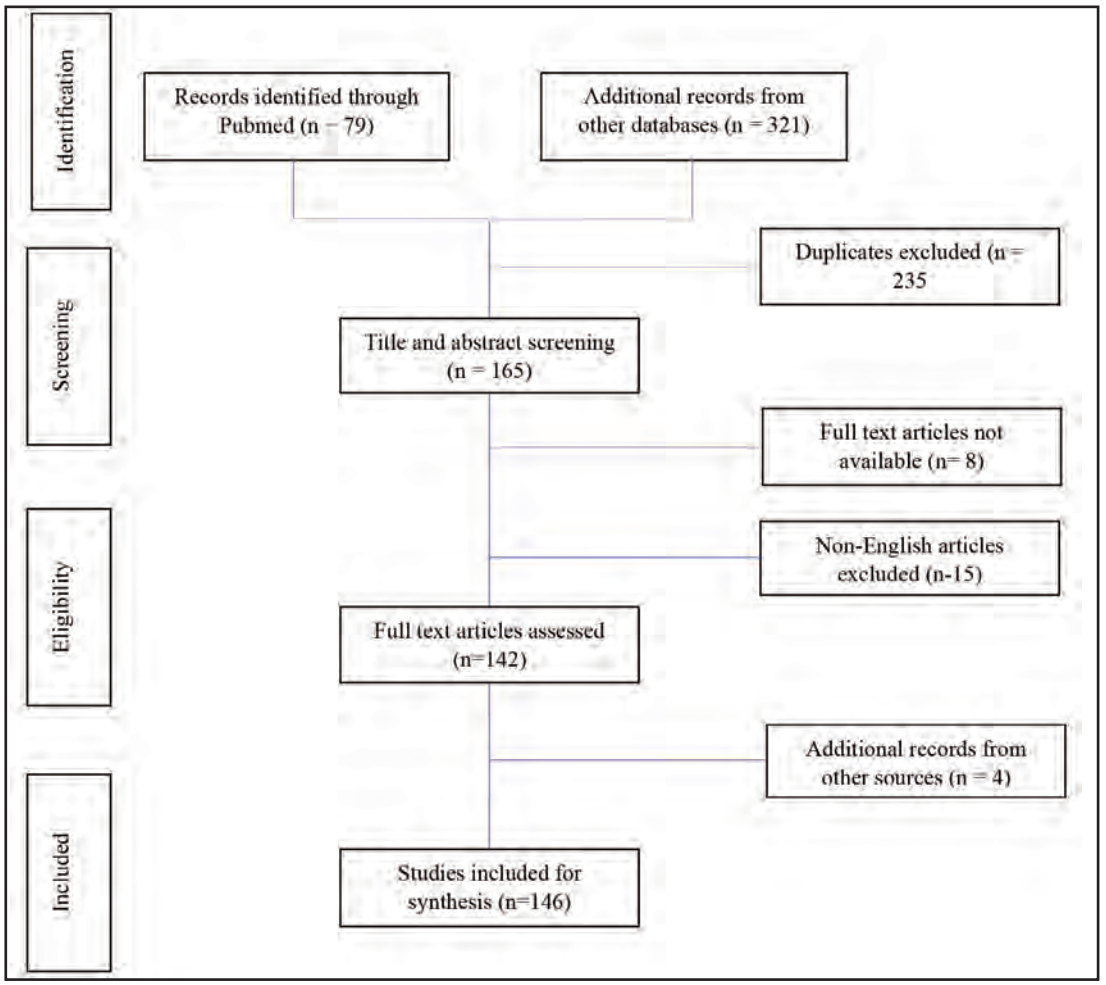

Fig. 1: PRISMA flow diagram of the study selection process

trimester with 84.8% of the incident diagnosed at term. The median gestational age of torsion in cases with no identifiable associated factor is 36 weeks (IQR = 33.2 to 38.0) while torsion in the uterus with fibromyomata(s), the median gestation is 38 weeks (IQR = 36.0 to 39.0). Torsion presented earlier when it is associated with Müllerian tube abnormality; as early as 8 weeks pregnancy with the median gestation at diagnosis of 26.5 weeks (IQR = 21.2 to 32.8). Two women had recurrent uterine torsions in successive pregnancies, all occurring in the third trimester.[89,98]

More than half of the women (59.3%) had at least one symptom at their presentation with the most common complaint being abdominal pain of varying severity. A large majority of the cases (85.3%) had at least one clinical sign and the most encountered were abdominal tenderness and/or rigidity followed by intrauterine fetal demise and shock (Table I). There were no specific signs of uterine torsion in pregnancy but change in placenta locations and extreme deviation of cervix are highly suggestive.[20,34,55,69,90,99-102]

Dextrotorsion was 1.5 times more common compared with the opposite turn and almost 2/3 of the cases had 180° torsion. A significant number of cases were associated with pelvic organ pathology, abnormal fetal lie or external uterine manipulation, with uterine fibroid and Müllerian tube abnormality being the most common (Table I). However, 40% of the torsions were found in normal uterus with a single fetus in the longitudinal lie and with no identifiable precipitating factor.

Two cases were identified before surgery and both were torsion of the rudimentary horns of unicornuate uterus, diagnosed by magnetic resonance imaging (MRI).[35,103] All cases underwent laparotomy except for a woman who had a laparoscopic examination at 8 weeks of pregnancy and another torsion was detected at postmortem examination.[35,104] Despite so, 36.2% (51/141) of the torsions were not diagnosed before hysterotomy and removal of the product of conception (Table II).

Emergency surgeries were performed for various indications in more than 80% of the cases, whereas the rest were planned surgeries. All cases had surgical removal of the product of conception either through hysterotomy, resection of the uterine horn (cornuate uterus) or hysterectomy, except for in two cases where detorsion was performed and the pregnancies were allowed to progressed resulting in livebirths.[105,106] Lower segment and transverse hysterotomy were performed majority of the cases but 2/3 of the incision

Table I: signs and symptoms associated with uterine torsion

	Number	%
1st trimester	3	2.0
2nd trimester	19	12.7
3rd trimester	129	85.3
Nulliparous	40/ 144	27.8
Previous scar	50/145	34.5
fetus lie		
Longitudinal	65/97	67.0
Transverse	27/97	27.1
Oblique	5/97	5.2
Symptoms		
Abdominal pain	79/150	52.7
Nausea/ vomiting	20/150	13.3
Reduced fetal movement	18/150	12.0
Vaginal bleeding	8/150	5.3
Asymptomatic	61/150	40.7
Signs		
Tenderness/ rigidity	48/150	32.0
Intrauterine fetal death†	45/142	31.7
Shock	33/150	22.0
Uterus larger than gestation	13/150	8.7
Fetal distress	19/141	13.5
Absent sign	22/150	14.7
Torsion characteristics		
Right	71/118	60.2
Left	47/118	39.8
Degree of torsion		
<180°	28/140	20.0
180°	99/140	70.7
>180°	13/140	9.3
Associated pathology		
Uterine fibroid	25/150	16.7
Müllerian tube abnormality	20/150	13.3
Twin	8/150	5.3
Adhesion	8/150	4.7
ECV/ massage	5/150	3.3
Ehler Danlos Syndrome	2/150	1.3
None	60/150	40.0

†= pregnancy at 22 completed weeks or more
ECV = external cephalic version

was on the posterior uterine wall. There were cases that required additional surgical procedures other than hysterotomy, mainly to control the haemorrhage, such as uterine compression suture, vascular ligations, hemi or subtotal hysterectomy and total hysterectomy (Table II). There were also two cases of hysterectomy with the fetus in situ because the surgeons judged that hysterotomy could cause excessive hemorrhage.[44,107]

Maternal and perinatal mortality

In this review, three cases of maternal mortality related to uterine torsion were reported. One woman died from shock while awaiting surgery for transverse fetal lie at term and the uterine torsion was diagnosed in the postmortem examination.[104] The other two were postpartum deaths; one was from the complications of massive postpartum haemorrhage secondary to severe placental abruption and uterine atony at 25 weeks of pregnancy.[39] Another maternal death occurred on third postoperative day for suspected massive pulmonary embolism, after a uterine torsion complicated by abruptio placentae at 36 weeks of gestation.[108] In all three cases, the uterus rotated 180° and both postpartum deaths occurred after a stormy perioperative period including subtotal hysterectomies and massive blood losses. With these data, the maternal mortality rate in this review stands at 2.0%.

A total of 141 torsions were diagnosed at 22 weeks gestation or beyond and there were 39 cases of stillbirths and 3 neonatal deaths; hence the perinatal mortality rate was 38.2%. One of the neonatal deaths was due to extreme prematurity, after the delivery at 25 weeks of gestation and two infants had severe intrauterine hypoxia, delivered at 30 and 33 weeks of gestation.[91,101,109] In uterine torsion of < 180°, 180°and >180°, the proportion of perinatal death was 20.0%, 35.9% and 81.8% respectively.

DISCUSSION

Owing to its rarity, it is impossible to describe the best course of action for uterine torsion in pregnancy without conducting a proper literature review. To date, there have been a few major reviews; Robinson and Duval in 1931, Nesbitt & Corner in 1956, Jensen in 1992, Wilson et al in 2006,

Table II: Surgical characteristics, maternal and perinatal outcomes

	Number	%
Emergency surgery	125	83.3
Elective surgery	25	16.7
Diagnosis at surgery		
Diagnosed prior to hysterotomy/ hysterectomy	91/141	64.5
Diagnosis after hysterotomy	50/141	35.5
Detorsion attempt		
Successful	35/129	27.1
Unsuccessful	46/129	35.7
Not attempted	48/129	37.2
Indication for surgery		
Abruptio / uterine rupture	46/145	31.7
fetal distress†	20/145	13.8
Transverse lie	15/145	10.3
Failed IOL/ poor progress	12/145	8.3
Scar dehiscence	5/145	3.4
Position of hysterotomy		
Anterior uterine wall	42/134	31.3
Posterior uterine wall	90/134	67.2
Fundal	2/134	1.5
Location of hysterotomy		
Lower segment	101/118	85.6
Upper segment	17/118	14.4
Type of hysterotomy		
Transverse	99/124	79.8
Vertical	23/124	18.5
J or T incision	2/124	1.6
Additional procedure		
B-lynch brace suture	3/150	2.0
Uterine artery ligation	5/150	3.3
Internal iliac artery ligation	1/150	0.7
Subtotal hysterectomy	9/150	6.0
Hemihysterectomy	3/150	2.0
Total hysterectomy	6/150	4.0
Resection of uterine horn	7/150	4.7
Myomectomy	7/150	4.7
Plication of round / uterosacral ligaments	8/150	5.3
Maternal outcome/ complication		
Abruptio placentae	39/150	26.0
Uterine atony	25/150	16.7
Uterine rupture	3/150	2.0
Maternal death	3/150	2.0
Perinatal Outcome		
Intrauterine fetal death†	39/110	35.5
Neonatal death	3/71	4.2
Perinatal death†	42/110	38.2

† = pregnancy at 22 completed weeks or more
IOL = induction of labour

Ramseyer et al in 2020 and a systematic review by Ferrari et al in 2021.[3,6-9,110] In the 1992 review, 212 cases were discussed and additional 66 cases were later added by other authors up to 2021. By extending the search outside of PubMed, we were able to locate 85 more publications for this review which included 87 cases. The main advantage of this review is the search methodology, which follows the PRISMA guidelines for systematic reviews and includes reports from databases and repositories beyond the PubMed. Expanding the search to also include non-indexed reports allows us to discuss more cases not captured in previous reviews, where 46% of these were located outside PubMed. Even though some of publications were not peer-reviewed, the information from these publications is still helpful, and we performed a risk assessment to ensure the included articles have acceptable bias levels. This review does have its limitations, namely the exclusion of non-English literatures and the nonavailability of some papers. The analysis was also limited in certain aspects since some reports did not include data of our interest especially the perinatal outcomes, which leads to different denominators in some of the parameters.

The assertions made by Barozzi and Robinson that "no tumour, no torsion" and "no uterine abnormalities, no torsion" respectively were based on the long-held belief that uterine torsion is uncommon in normal pelvic anatomy.[110] Nesbitt & Comer, on the other hand, proposed that the association should be "no pelvic pathology, torsion unlikely".[3] In the non-gravid uterine torsion, 84.6% of the cases were linked to either an ovarian tumour or uterine fibroid.[111] These correlations were observed to a lower extent during pregnancy, with only 30.8% of cases were associated with uterine fibroids and Müllerian tube abnormalities. In 63.8% of the cases, no anatomical abnormalities in the pelvis or abdomen were reported. Torsion in pregnancy had been reported as early as 6 weeks, and up to 43 weeks of

pregnancy.[8] In Müllerian tube abnormalities, more than half presented in the 1st and 2nd trimester while in normal or fibromatous uterus, almost 90% of torsion occurred in 3rd trimester. The tendency of the torsion occurring in the later gestations is explained by the weight of the uterus and the softening of the uterine isthmus in advance pregnancy. Of the identifiable associated factors for uterine torsion in pregnancy, the most commonly encountered are the abnormal fetal lie (33%) followed by the uterine fibroid (17.3%) and Müllerian duct abnormalities (13.3%). Few authors proposed that uterine torsion could be caused by fetal transverse lie.[59,72,101] On the other hand, the non-longitudinal lie could in fact be one of the presentations of uterine torsion, where the contracted lower segment prevents the fetal presenting part from descending toward the pelvis. A case describing an immediate change in fetal lie from transverse to longitudinal right after uterine detorsion lends weight to this.[72] With these analyses, 37.8% of the cases had no identifiable predisposing and/or activating factor.

It is anticipated that torsion along the uterine axis will result in venous compression and vascular engorgement, which may trigger ischemia and placental abruption. These could manifest in a wide range of symptoms, the most frequently reported being abdominal pain. Patients could also present with uterine tenderness or rigidity, signs of fetal distress, stillbirths or even hypovolemic shock. Eight women were in shock but had no evidence of placental abruption, which suggests that the origin was neurogenic.[52,66,81,91,104,112-114] Some also presented with a uterine size larger than the gestation and 2/3 were associated with abruptio placentae, while the rest were likely due to the extensive venous congestion.[91,112] Overall, 40% of the cases were asymptomatic and 16.3% had no clinical sign.

Previous authors have described numerous signs said to be diagnostic of uterine torsion such as pulsation in the anterior vaginal fornix, demonstration of spiral vagina, displacement of the urethra, bladder and/ or rectum.[3,110,115] With the exception of a woman with 120° torsion, in which an MRI revealed the twisted upper vagina, none of the cases included in this review had any specific clinical finding as stated above.[99] However, a few cases of extreme cervical displacement had been detected by clinical examination and MRI. Majority of the cases had no cervical changes as most torsion occurred at the cervicouterine junction, and the cervix is kept stable by the Mackenrodt's and the uterosacral ligaments. In Müllerian tube abnormalities, torsion usually involves only a part of the uterus and may not exert enough torque to twist the cervix and the upper vagina.

Making the correct initial diagnosis of uterine torsion when a pregnant woman presents with an acute abdominal incident is not of the upmost importance since surgery will still be carried out. But delaying the surgery in subacute or chronic uterine torsion may put the mother and the unborn child in peril. The diagnosis of uterine torsion in pregnancy has almost always been an intraoperative diagnosis, except in a few instances. A case of 90° torsion in active labour was diagnosed when the round ligament was felt across the thin anterior abdominal wall. The application of manual detorsion and abdominal binder allowed the labour, previously associated with ineffective contraction, to progress.[4] In non-pregnant torsion, computerized tomography (CT) scans and MRI have been used extensively. A review by Matsumoto et al. found that about 70% of the cases had undergone CT scans and/or MRI prior to surgery, and the cervix's "whirl sign" has a 44% sensitivity with 100% positive predictive value for uterine torsion outside the pregnancy.[111] In pregnancy, the use of MRI had reported changes in the cervix and upper vagina, although in most cases, the correlation with uterine torsion was made retrospectively after the laparotomy.[20,34,35,99,103]

In veterinary obstetrics, uterine artery Doppler had been used to diagnose uterine torsion in does and buffaloes.[116,117] Doppler study of the uterine vessels could be incorporated in humans and should be further investigated, such as demonstrating uterine vessels crossing the uterine midline or encircling the isthmus, abnormally dilated vessels or abnormal uterine artery Doppler indices. In fact, engorgement of myometrial vein had been demonstrated in a non-gravid uterine torsion, suggesting that the vascular changes could potentially be a diagnostic parameter in pregnancy.[118] One of the more suggestive signs of gravid uterine torsion is the change in placental locations, seen on ultrasound or MRI. The condition, also called placenta migran, was first reported in 1989 where the ultrasound findings were initially disregarded as documentation error.[119] In few cases including ours, the change in placental locations was not noticed before the caesarean section, hence missing a diagnostic opportunity before the surgery.[47,55,101,120] It is suggested that the change in placental location should be sought in unexplained abdominal pain or suspected abruptio placentae which might indicate uterine torsion. Some authors proposed that placenta location should be determined after every external cephalic version attempt or in case of uterine didelphys.[102,121] This, however, might not be seen in all situations, such as in fundal placenta or in 360° torsion.

The mainstay of the management is relieving the vascular occlusion due to the torsion and delivery of the fetus when necessary. Uterine detorsion not only restores the placental circulation but may also improves the maternal condition. This change was almost immediate with rising blood pressure and a reduction in heart rate after returning the uterus to its normal position.[70] However, only 43.2% of the detorsion attempts were successful. Failure to diagnose or failed detorsion may lead to hysterotomy on the posterior uterine wall, which should be avoided as the scar integrity in the subsequent pregnancy is not known. In most cases where the torsion was not immediately diagnosed at surgery, the uterovesical fold was either not identified or the bladder flap was not seen.[7,38,49,77, 121-124] There were also cases where the bladder flap could not be made, although no further explanation offered by the authors.[63,115,126] Current data suggest that bladder flap may be omitted in lower segment caesarean section which may reduce the operating time.[126] Yet, identifying the vesicouterine reflection is still important as to ensure the proper placement of the hysterotomy incision especially in uterine torsion.

In the 1992 review, 19 cases of maternal death related to uterine torsion were recorded, with only one reported after 1960.[6] From there on, three more cases of maternal deaths related to uterine torsion were reported in 2005, 2013 and 2020 but only one was discussed in previous reviews, as the other two cases were not indexed in PubMed.[7-9] Two of the deaths occurred after the caesarean delivery, related to the complications of massive postpartum haemorrhage in association with placental abruption.[39,108] The other, an antepartum death, was likely due to severe neurogenic shock as the postmortem examination did not show any sign of uterine rupture nor retroplacental hematoma.[104] Despite the current advancement in modern medicine, perinatal mortality in uterine torsion did not show significant improvement. Stillbirths contributed to more than 95% of perinatal deaths and most of them were due to abruptio placentae. The overall mortality rate before 1956 was 30.4% and was reported to be lower at 18% and 22% in 2006 and 2020 reviews respectively.[3,7,8] We found in this review, the perinatal mortality is higher at 38.2%, probably due to our search methodology including publications from various sources.

Based on the available information, we would encourage obstetricians who encounter pregnancies with unexplained abdominal pain, placental abruption with or without fetal effect, to consider uterine torsion as a possible cause of the presenting signs and symptoms. Supporting evidence such as the change in placenta locations on ultrasound and abnormally located or deviated cervix should be sought after. If time permits, Doppler examination of the uterine vessels or MRI should also be performed as predelivery diagnosis could help plan the appropriate course of action for the patient.

CONCLUSION

Uterine torsion, a rare pathological condition in pregnancy, carries significant risk to both the pregnant woman and her fetus. Diagnosing it during pregnancy before laparotomy remains a challenge but evidence suggest some potential methodologies that could be helpful.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Appendix 1

JBI Critical Appraisal Check list for Case Reports[11]

Ref	Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
7	Wilson et al	yes	yes	yes	yes	yes	yes	yes	yes
9	Ferrari et al	yes	yes	yes	yes	yes	yes	yes	yes
13	Mulvey & Turner	yes	yes	yes	yes	yes	yes	yes	yes
14	Aviram et al	yes	yes	yes	yes	yes	yes	yes	yes
15	Sanusi & Simanowitz	yes	yes	yes	yes	yes	yes	yes	yes
16	Ghosh & McKenna	yes	yes	yes	yes	yes	no	no	no
17	Olah	yes	yes	yes	yes	yes	yes	yes	yes
18	Sharma et al	yes	yes	yes	yes	yes	yes	yes	yes
19	Masood et al	yes	yes	yes	yes	yes	yes	yes	yes
20	Picone et al	yes	yes	yes	yes	yes	yes	yes	yes
21	Dalal et al	yes	yes	yes	yes	yes	yes	yes	yes
22	Hariharan et al	yes	yes	yes	yes	yes	yes	yes	yes
23	Jahan et al	yes	yes	yes	yes	yes	yes	yes	yes
24	Mihu et al	yes	yes	yes	yes	yes	yes	yes	yes
25	Prabhakar & Gupta	yes	yes	yes	yes	yes	yes	yes	yes
26	Waghmare	yes	yes	yes	yes	yes	yes	yes	yes
27	Kamanu et al	yes	yes	yes	yes	yes	yes	yes	yes
28	Meharunnissa et al	yes	yes	yes	yes	yes	no	yes	yes
29	Ahsan & Humayun	yes	yes	yes	yes	yes	yes	yes	yes
30	Moustafa et al	yes	yes	yes	yes	yes	no	yes	yes
31	Naik et al	yes	yes	yes	yes	yes	yes	yes	yes
32	Rasquiha et al	yes	yes	yes	yes	yes	no	yes	yes
33	Acharya & Mohapatra	yes	yes	unclear	yes	yes	yes	yes	yes
34	Bissa & Shyam	yes	yes	yes	yes	yes	yes	yes	yes
35	Blyth	yes	yes	yes	yes	yes	yes	yes	yes
36	Dragosloveanu	yes	yes	yes	yes	yes	yes	yes	yes
37	Jain et al	yes	yes	yes	yes	yes	yes	yes	yes
38	Krishnaveni & Saraswathi	yes	yes	yes	yes	yes	yes	yes	yes
39	Qureshi et al	yes	yes	yes	yes	yes	yes	yes	yes
40	Tehrani et al	yes	yes	yes	yes	yes	yes	yes	yes
41	Tripathi & Tripathi	yes	yes	yes	yes	yes	yes	yes	yes
42	Boynukalin et al	yes	yes	yes	yes	yes	no	yes	yes
43	Rathod	yes	yes	yes	yes	yes	yes	yes	yes
44	Inderjeet et al	yes	yes	yes	yes	yes	yes	yes	yes
45	Jayanthi & Rao	yes	yes	yes	yes	yes	yes	yes	yes
46	Melchor& Dela Concepcion-Co	yes	yes	yes	yes	yes	yes	yes	yes
47	Varsha et al	yes	yes	yes	yes	yes	yes	yes	yes
48	Alhassan et al	yes	yes	yes	yes	yes	yes	yes	yes
49	Choi & Lee	yes	yes	yes	yes	yes	yes	yes	yes
50	Chundawat et al	yes	yes	yes	yes	yes	yes	yes	yes
51	Feizal et al	yes	yes	yes	yes	yes	yes	yes	yes
52	Jalvee & Kadrekar	yes	yes	yes	yes	yes	yes	yes	yes
53	Parmar et al	yes	yes	yes	yes	yes	yes	yes	yes
54	Protrka et al	yes	yes	yes	yes	yes	yes	yes	yes
55	Vijayakumar et al	yes	yes	yes	yes	yes	yes	yes	yes
56	Anne et al	yes	yes	yes	yes	yes	yes	yes	yes
57	Cetin et al	yes	yes	yes	yes	yes	yes	yes	yes
58	Goswami & Gautam	yes	yes	yes	yes	yes	yes	yes	yes
59	Abdulaal et al	yes	yes	yes	yes	yes	yes	yes	yes
60	Komatsu et al	yes	yes	yes	yes	yes	unclear	yes	yes
61	Magembe	yes	yes	yes	yes	yes	yes	yes	yes
62	Patra et al	yes	yes	yes	yes	yes	yes	yes	yes
63	Thanappan	yes	yes	yes	yes	yes	yes	yes	yes
64	Dasari et al	yes	yes	yes	yes	yes	yes	yes	yes
65	Ramya	yes	yes	yes	yes	yes	yes	yes	yes
66	Zeng et al	yes	yes	yes	yes	yes	yes	yes	no
67	Bagli & Erdem	yes	yes	yes	yes	yes	yes	yes	yes
68	Filippo et al	yes	yes	yes	yes	yes	yes	yes	yes
69	Gross et al	yes	yes	yes	yes	yes	yes	yes	yes
70	Ikram ul Haq	yes	yes	yes	yes	yes	yes	yes	yes
71	Kocher & Hirsig	yes	yes	yes	yes	yes	yes	yes	yes
72	Mangirish et al	yes	yes	yes	yes	yes	yes	yes	yes
73	Mayadeo Mayadeo & Devalla	yes	yes	yes	yes	yes	yes	yes	yes
74	Mokhtar et al	yes	yes	yes	yes	yes	yes	yes	yes
75	Narayanan et al	yes	yes	yes	yes	yes	yes	yes	yes
76	Tanouti et al	yes	yes	yes	yes	yes	yes	yes	yes

Ref	Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
77	Yin et al	yes	yes	yes	yes	yes	yes	yes	yes
78	Agrawal et al	yes	yes	yes	yes	yes	yes	yes	yes
79	Benor & Tetelman	yes	yes	yes	yes	yes	yes	yes	yes
80	Chau et al	yes	yes	yes	yes	yes	yes	yes	yes
81	Gaboura et al	yes	yes	yes	yes	yes	yes	yes	yes
82	Gadappa et al	yes	yes	yes	yes	yes	no	yes	yes
83	Huynh & Anderson	yes	yes	yes	yes	yes	yes	yes	yes
84	Khan et al	yes	yes	yes	yes	yes	yes	yes	yes
85	Makwe et al	yes	yes	yes	yes	yes	yes	yes	yes
86	Othman Al Tarifi et al	yes	yes	yes	yes	yes	yes	yes	yes
87	Somani et al	yes	yes	yes	yes	yes	yes	yes	yes
88	Wan Adnan et al	yes	yes	yes	yes	yes	yes	yes	yes
89	Boogaerts et al	yes	yes	yes	yes	yes	yes	yes	yes
90	Bouattour et al	yes	yes	yes	yes	yes	yes	yes	yes
91	Ghalandarpoor-Attar & Ghalandarpoor-Attar	yes	yes	yes	yes	yes	yes	yes	yes
92	Hendriks et al	yes	yes	yes	yes	yes	yes	yes	yes
93	Mansour et al	yes	yes	yes	yes	yes	yes	yes	yes
94	Onyekpa et al	yes	yes	yes	yes	yes	yes	yes	yes
95	Singh et al	yes	yes	yes	yes	yes	no	yes	yes
96	Slaoui et al	yes	yes	yes	yes	yes	yes	yes	yes
97	Vuong & Nguyen	yes	yes	yes	yes	yes	yes	yes	yes
98	Berger et al	yes	yes	yes	yes	no	no	no	no
99	Nicholson et al	yes	yes	yes	yes	yes	yes	yes	yes
100	Albayrak et al	yes	yes	yes	yes	yes	yes	yes	yes
101	Zullino et al	yes	yes	yes	yes	yes	yes	yes	yes
102	Demaria et al	yes	yes	yes	yes	yes	yes	yes	yes
103	Singh et al	yes	yes	yes	yes	yes	yes	yes	yes
104	Guie et al	yes	yes	yes	yes	yes	yes	yes	yes
105	Bukar et al	yes	yes	yes	yes	yes	yes	yes	yes
106	Kopko et al	yes	yes	yes	yes	yes	yes	yes	yes
107	Alpana & Meenaxi	yes	yes	yes	yes	yes	yes	yes	yes
108	Darido et al	yes	yes	yes	yes	yes	yes	yes	yes
109	LaHood & You	yes	yes	yes	yes	yes	yes	yes	yes
112	Fatih et al	yes	yes	yes	yes	yes	yes	yes	yes
113	Arumugham et al	yes	yes	yes	yes	yes	yes	yes	yes
114	Moores et al	yes	yes	yes	yes	yes	no	yes	yes
115	Duplantier et al	yes	yes	yes	yes	yes	yes	yes	yes
120	Ulu et al	yes	yes	yes	yes	yes	yes	yes	yes
121	Salani et al	yes	yes	yes	yes	yes	yes	yes	yes
122	Basava et al	yes	yes	yes	yes	yes	yes	yes	yes
123	Poulose et al	yes	yes	yes	yes	yes	yes	yes	yes
124	Sapric & Lazoric	yes	yes	yes	yes	yes	yes	yes	yes
125	Ahmed et al	unclear	yes	yes	yes	yes	yes	yes	yes
127	Bolaji et al	yes	yes	yes	yes	yes	yes	yes	no
128	Olah	yes	yes	yes	yes	yes	yes	yes	yes
129	Fait et al	yes	yes	yes	yes	yes	yes	yes	yes
131	O'Connor & Hurley	yes	yes	yes	yes	yes	yes	yes	yes
132	Pelosi III & Pelosi	yes	yes	yes	yes	yes	yes	yes	yes
133	Achanna et al	yes	yes	yes	yes	yes	yes	yes	yes
134	Kovavisarach & Vanitchanon	yes	yes	yes	yes	yes	yes	yes	yes
135	Mustafa et al	yes	yes	yes	yes	yes	yes	yes	yes
136	Kim et al	yes	yes	yes	yes	yes	yes	yes	yes
137	Rich & Stokes	yes	yes	yes	yes	yes	yes	yes	yes
138	Rudloff & Joels	yes	yes	yes	yes	yes	yes	yes	yes
139	El-Taher & Hussein	yes	yes	yes	yes	yes	yes	yes	yes
140	Cook & Jenkins	yes	yes	yes	yes	yes	yes	yes	yes
141	Dandawate & Carpenter	yes	yes	yes	yes	yes	yes	yes	yes
142	Munro et al	yes	yes	yes	yes	yes	yes	yes	yes
143	Joseph et al	yes	yes	yes	yes	yes	yes	yes	yes
144	Metz et al	yes	yes	yes	yes	yes	yes	yes	yes
145	De Ioris et al	yes	yes	yes	yes	yes	yes	yes	yes
146	Deshpande et al	yes	yes	yes	yes	yes	yes	yes	yes
146	Wang et al	yes	yes	yes	yes	yes	yes	yes	yes
147	Zhang & Wimalasundera	yes	yes	yes	yes	yes	yes	yes	yes
148	Erdogdu et al	yes	yes	yes	yes	yes	yes	yes	yes
149	Homam et al	yes	yes	yes	yes	yes	yes	yes	yes
150	Farhadifar et al	yes	yes	yes	yes	yes	no	yes	yes
151	Rood & Markham	yes	yes	yes	yes	yes	yes	yes	yes

Ref	Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
152	Sachan et al	yes	yes	yes	yes	yes	yes	yes	yes
153	Vavrinkova & BInder	yes	yes	yes	yes	yes	yes	yes	yes
154	Nash et al	yes	yes	yes	yes	yes	no	yes	yes
155	Karavani et al	yes	yes	yes	yes	yes	yes	yes	yes
156	Carrier et al	yes	yes	yes	yes	yes	yes	yes	yes
157	Hoffman & Jayaratnam	yes	yes	yes	yes	yes	no	yes	yes
158	Kilicci et al	yes	yes	yes	yes	yes	yes	yes	yes
159	Kumar et al	yes	yes	yes	yes	yes	yes	yes	yes
160	Gupta et al	yes	yes	yes	yes	yes	yes	yes	yes
161	Toshniwal	yes	yes	yes	yes	yes	yes	yes	yes

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Non-statin therapy in patients with elevated LDL-C and high platelet reactivity: a narrative review

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ABSTRACT

Introduction: Evidence of an association between elevated LDL-C levels and HRPR - which are highly prevalent separately and both lead to rapid progression of atherosclerosis on ineffective hypolipidaemic therapy - is scarce.

Materials and Methods: We searched electronic databases. All available randomized controlled trials (RCTs) were included, and we considered the scientific novelty of the study, the reliability of the reported study results; the high methodological level of the study of non-statin therapy in patients with dyslipidemia and high residual platelet reactivity, with no language or date restrictions. We did separate random-effects meta-analyses for LDL-C, HRRP on their effects on LDL-C levels and outcomes, taking into account the reliability of the reported study results and the high methodological level of the study. The challenge of achieving target LDL-C levels, their impact on high residual platelet reactivity, and the choice of optimal antiplatelet and lipid-lowering therapy remains unresolved.

Results: The integration of newer therapies, such as inclisiran and PCSK9 inhibitors, may play a critical role in achieving optimal outcomes for patients at high cardiovascular risk.

Conclusion: The necessity of applying an individual multidisciplinary approach in order to determine the best regimen of antiplatelet and lipid-lowering therapy in patients with coronary heart disease, including after revascularization, is shown. This approach will reduce the risk of recurrent cardiovascular events. Few studies on the relationship between LDL-C and HRPR dictate the need for more detailed research in this area.

KEYWORDS:
low-density lipoproteins cholesterol, high residual platelet reactivity, non statin lipid-lowering therapy

INTRODUCTION

Nowadays, cardiovascular diseases, despite the achievements of modern cardiology, are the leading cause of mortality throughout the world. In 2015, it was found that cardiovascular pathology causes one third of all deaths, especially from coronary heart disease (CHD) in economically developed countries. Low-density lipoprotein cholesterol (LDL-C) has been identified as a major risk factor for cardiovascular disease, associated with one in four deaths from CHD in patients with high LDL-C levels.[1,2] In general, elevated LDL-C is considered a modifiable risk factor for the development of cardiovascular diseases, playing a major role in the pathogenesis of atherosclerosis.[3,4]

High residual platelet reactivity (HRPR) is a predictor of many adverse cardiovascular complications, such as myocardial infarction, stent thrombosis in patients with coronary artery disease (CAD), and death from cardiovascular diseases.[5,6] Considering the involvement of platelets and LDL-C in the pathogenesis of atherosclerosis, it can be assumed that high residual platelet aggregation (HRAP) is capable of increasing the proliferation of smooth muscle cells, forming foam cells, which, by absorbing LDL-C, contribute to the formation of atherosclerotic plaque. Therefore, reducing the level of platelet aggregation and LDL-C by prescribing antiplatelet and lipid-lowering therapy can block the process of atherogenesis and subsequent cardiovascular complications.

Patients with elevated LDL-C and high residual platelet reactivity (HRPR) are a difficult group for cardiologists, cardiovascular surgeons and endovascular surgeons. Evidence of an association between elevated LDL-C levels and HRPR - which are highly prevalent separately and both lead to rapid progression of atherosclerosis, high rates of recurrent arterial thrombosis in cerebral and coronary vessels against a background of polymorbidity, including in patients after revascularization procedures- is scarce.

The study provides an overview of modern clinical studies on the treatment of patients with elevated LDL-C in cardiovascular diseases (CVD), as well as their effect on HRPR, achieving target LDL-C levels in very high-risk patients with HRPR during antiplatelet therapy. This study employs a narrative literature review to achieve two main objectives (1) to examine the effect of non-statin therapy on lowering LDL values in atherosclerosis-associated disease, including very

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high-risk patients with high residual platelet reactivity; and (2) to determine the impact of target LDL values on high residual platelet reactivity in very high-risk patients with cardiovascular disease receiving antiplatelet therapy.

The secondary objective is to identify gaps and limitations in the existing literature on LDL lowering in patients with cardiovascular disease and high residual platelet reactivity and to suggest directions for future research, including exploring novel therapeutic interventions in the form of inclisiran, the long-term outcomes of treatment strategies to achieve target LDL levels, and approaches designed for patients at very high risk of cardiovascular events.

MATERIALS AND METHODS

Search strategy

A systematic literature search was conducted in the electronic PubMed, Embase, Scopus and Cochrane Library databases and forward and backward citations for studies published in English between January 10, 2014, and January 10, 2023 (Free full text).

The search strategy utilized relevant keywords and Medical Subject Headings (MeSH) to comprehensively search for studies related to non-statin therapy for cardiovascular disease. The primary keywords included: "low-density lipoproteins cholesterol", "high residual platelet reactivity", "non statin lipid-lowering therapy".

Study selection criteria

The inclusion criteria covered studies that were published in peer-reviewed journals that included adults with dyslipidemia on a background of atherosclerosis-associated disease and/or coronary heart disease. Both observational studies (cross-sectional, cohort, case control) and interventional studies (clinical trials, interventions) were considered. All available randomized controlled trials (RCTs) were included, and we considered the scientific novelty of the study, the reliability of the reported study results; the high methodological level of the study of non-statin therapy in patients with dyslipidemia and high residual platelet reactivity, with no language or date restrictions. We did separate random-effects meta-analyses for LDL-C, HRRP on their effects on LDL-C levels and outcomes, taking into account the reliability of the reported study results and the high methodological level of the study.

Exclusion criteria. The exclusion criteria included studies that were not published in English, studies focused exclusively on non-dyslipidemic populations, and studies with small sample sizes or incomplete data with small sample sizes or incomplete data. Non-original articles, such as commentaries, editorials, reviews, and letters to the editor, were excluded.

Data extraction, synthesis and analysis

Data extraction was conducted independently by three reviewers, using a standardized form. Data extraction fields included study characteristics (author, year, country(s), purpose, design, sample size, patient demographics), non-statin therapy including studies with inclisiran, LDL levels in patients with dyslipidemia, prevalence rates of not achieving treatment goal and cardiovascular events on therapy. A narrative synthesis approach was employed to summarise and integrate the findings across the selected studies.

Quality assessment

The quality of included studies was assessed using established tools such as the Newcastle-Ottawa Scale for Observational Studies and the Cochrane Collaboration Risk of Bias Tool for interventional studies. This assessment helped ensured the validity and reliability of the evidence synthesized. A critical appraisal was conducted for each study by two independent researchers of this paper. Any disagreements were resolved through discussion with the third author.

RESULTS

The selection process is illustrated in the PRISMA flow diagram (Figure 1).

Study characteristics

Several studies have described the indirect effects of lowering LDL-C in atherosclerotic plaque and platelet aggregation. The direct effect of lipid-lowering therapy on platelet function was also examined. In vitro incubation of platelets and lipoproteins shows how high levels of LDL-C activate platelet aggregation. In particular, apoB-100, expressed by LDL-C, binds to and activates the LDL-C receptor expressed by platelets and alters signal transduction. Platelets become more sensitive to activated stimuli and acquire a hyperaggregation phenotype.[7] In addition, platelets with higher mean platelet volume (MPV) are correlated with a higher risk of ischaemic and thrombosis.[7,8] Several studies have demonstrated a significant association between hyperlipidemia and platelet volume indices (PVI), including mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR).[8]

In accordance with the Systemic CoronarRisk Estimation (SCORE) scale. which assesses the risk of death from myocardial infarction, heart failure and stroke over the next ten years, patients are divided into four categories: low, moderate, high, very high risk. In recent years, another category has been added - extreme risk. This scale takes into account many modifiable risk factors: arterial hypertension, dyslipidaemia and smoking, as well as non-modifiable risk factors: gender and age.[9] Currently, the European Heart Association, based on its recommendations on atherosclerosis, considers that maintaining adequate lipoprotein control, especially lowering LDL levels, is important for the treatment of dyslipidemia. Lowering LDL-C levels is especially important in patients at high, very high, and extreme risk. The target LDL-C level according to the SCORE scale is: in patients at high risk - less than 1.8 mmol/L, very high risk - less than 1.4 mmol/L and extreme risk - less than 1 mmol/L.

According to European studies, 80% of very high-risk patients do not achieve target LDL-C levels with statin monotherapy.[10] Statin pharmacotherapy is the gold standard in the treatment of hypercholesterolaemia, especially LDL. Moreover, some patients do not achieve target levels even on

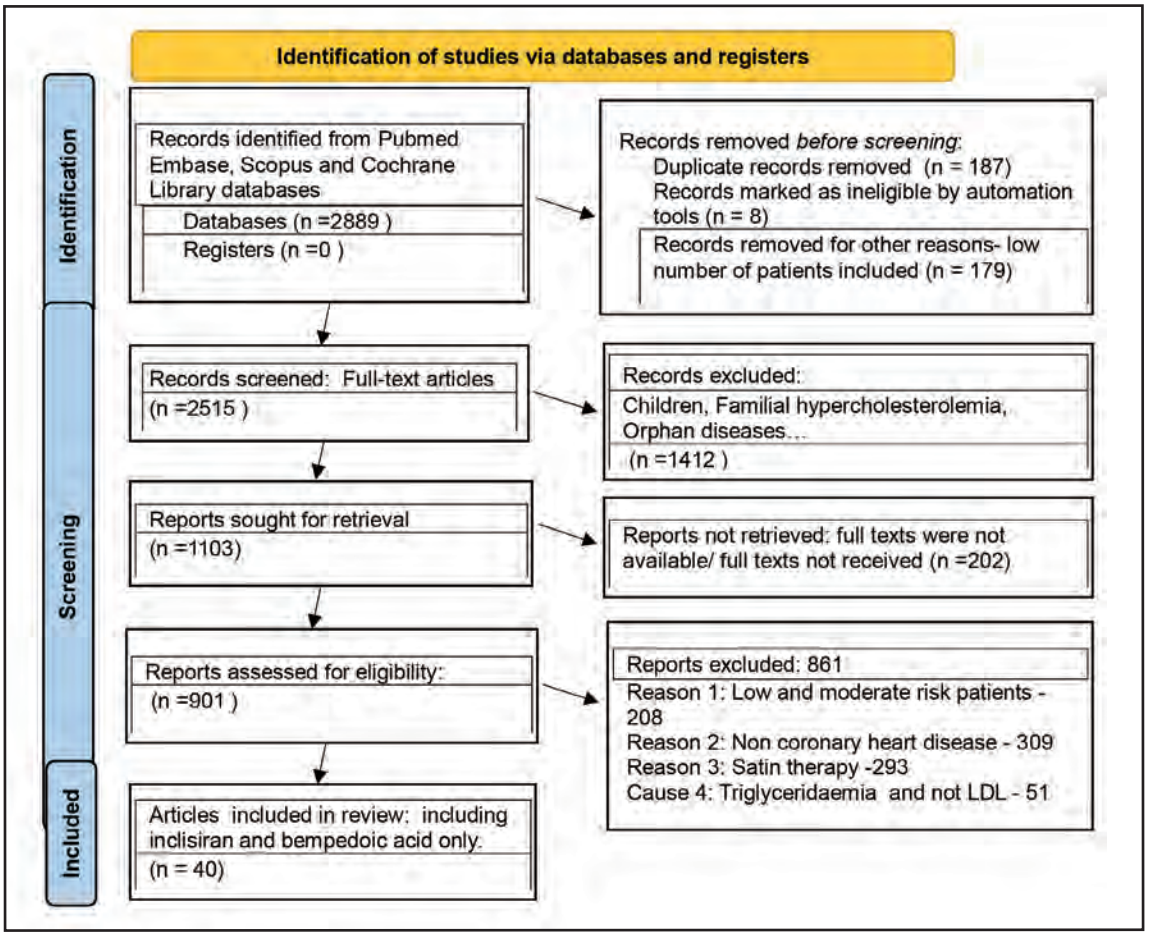

Fig. 1: PRISMA diagram of the screening process

high tolerated doses of statins.[11] In addition, long-term statin therapy is associated with side effects such as fibromyalgia and myopathy, which are the main reasons for stopping of lipid-lowering therapy.[10,12]

Currently, for patients who do not reach the target LDL level, a combination of statins with ezetimibe is recommended; if this combination is not enough to achieve the therapeutic goal, it is necessary to add monoclonal antibodies inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), in particular alirocumab, evolocumab.[13,14] A study by Murphy et al., which examined the comparative effectiveness of atorvastatin at a dose of 80 mg and pravastatin at a dose of 40 mg in patients with recent acute coronary syndrome, showed the benefits of high-dose statin therapy compared with a moderate dose.[16] PCSK9 inhibitors (evolocumab and alirocumab) reduce LDL levels by approximately 60% and are given once or twice a month subcutaneously.[17,18]

The FOURIER trial compared the efficacy of evolocumab with placebo in 27,564 patients with cardiovascular disease. After 48 weeks of evolocumab therapy, patients experienced a 1.5% reduction in LDL cholesterol levels from 92 to 30 mg/dL, and a 1.5% reduction in absolute risk and cardiovascular events compared with statin therapy ($p < 0.001$).

Moreover, the ODYSSEY trial studied 18,924 high-risk patients who experienced acute coronary syndrome with LDL-C levels ≥1.8 mmol/L despite receiving the maximum dose of statin using alirocumab. Treatment with alirocumab was associated with a 61% reduction in LDL-C levels over 12 months, as well as a 15% reduction in major reversible cardiovascular events (HR, 0.85; 95% CI [0.78, 0.93]) and mortality. (HR, 0.85; 95% CI [0.73,0.98]) over a mean period of 2.8 years.[15,19,20]

The DESCARTES trial (long-term effect of PCSK9 monoclonal antibodies versus placebo study) showed that side effects (increased levels of creatine kinase above normal levels and muscle pain) were observed at similar levels in both groups (placebo and evolocumab).[21,22]

Bempedoic acid (BA) is an oral inhibitor of adenosine triphosphate (ATP) citrate lyase, an enzyme that acts "upstream" of the cholesterol synthesis cascade than HMG-CoA, which is the "target" of statins, catalyzing the production of acetyl coenzyme A, a precursor to the mevalonate pathway of cholesterol synthesis. The results of a 12-week randomized controlled trial indicate a reduction in LDL cholesterol levels by up to 30% with BA monotherapy and up to 50% when BA is combined with ezetimibe.[15,23] The main disadvantages of the drug are the development of gout and high cost.

Inclisiran is a cholesterol-lowering double-stranded small interfering RNA conjugated to an N-acetylgalactosamine (GalNAc) coding strand to facilitate uptake by hepatocytes. In hepatocytes, inclisiran uses the mechanism of RNA interference and triggers the catalytic decay of mRNA, acting on proprotein convertase subtilisin-kexin type 9 (PCSK-9). This helps to increase the recycling of the LDL cholesterol receptor and its expression on the surface of hepatocytes, which leads to an increase in the uptake of LDL cholesterol and a decrease in its concentration in the blood plasma. Inclisiran blocks the transcription of PCSK-9 intracellularly, which leads to a decrease in the production of PCSK-9 in hepatocytes, which leads to an increase in LDL-C receptors on the surface of hepatocytes, which take up LDL and reduce their amount in the blood.[13,24] According to atherosclerosis guidelines, inclisiran is a new non-statin drug that has been approved by the USA Food and Drug Administration and is prescribed twice a year 1,25. The main difference between monoclonal antibodies and inclisiran is that inclisiran acts intracellularly by activating LDL cholesterol receptors, while PCSK9 inhibitors act extracellularly by binding to and blocking circulating PCSK-9 protein.[1,26]

Adverse reactions of inclisiran. All adverse events were mild or moderate in severity and did not require discontinuation of the study in any participant. The main side effects are cough, musculoskeletal pain, headache, back pain, diarrhoea and nasopharyngitis.[21,27] One study participant taking a statin had asymptomatic increases in GGTP and ALT without increases in bilirubin; Enzyme levels returned to normal after stopping statins. In addition, some study participants experienced erythema and pain at the injection site. No changes in corrected QT interval (QTc) were observed.[21,28] The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea and dizziness. The incidence of these adverse events was not significant between the inclisiran and placebo groups.

The multicentre, double-blind, placebo-controlled ORION-1 trial included 501 patients with coronary artery disease with high LDL levels. The average age of the participants was 63 years. Overall, 73% of participants were receiving statin therapy. Patients were randomized to receive a single dose of placebo or 200, 300 and 500 mg of inclisiran or two doses of placebo (on days 1 and 90) or 100, 200 and 300 mg of inclisiran. The study assessed the percentage change in LDL cholesterol during treatment with different doses of inclisiran for 180 days. At day 180, there was a decrease in LDL cholesterol compared with placebo from 27.9% to 41.9% after a single dose of inclisiran and from 35.5% to 52.6% after a double dose ($p<0.001$ for all comparisons with placebo). The greatest reduction in levels was observed with the 2-dose inclisiran 300 mg regimen, which reduced LDL, PCSK-9, and C-reactive protein levels by 52.6% ($p < 0.001$), 69.1% ($p < 0.001$), and 16.7% ($p < 0.05$), respectively.[24,29]

Serious adverse events occurred in 11% of patients receiving inclisiran and 8% of those receiving placebo. Injection site reactions were observed in 4% and 7% of patients receiving one and two doses of inclisiran. The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhoea and dizziness. The incidence of these adverse events was not significant between the inclisiran and placebo groups.[24,30]

The ORION-2 study is a pilot study of the effect of inclisiran sodium in patients with familial homozygous hyperlipidaemia.[24] The study included 4 patients who had a genetically confirmed defect in coding the LDL receptor. After two doses of the drug, the duration of observation was 180 days. The decrease after six months in LDL-C ranged from -17.5 to -37.0%, and the decrease in plasma PCSK-9 concentration ranged from -40.5 to -80.5%. Follow-up for up to 10 months did not reveal any adverse events or laboratory abnormalities (except for those characterizing the intervention on lipid metabolism).[31,32]

ORION-3 is an extension study of ORION-1 with a 4-year follow-up period. At day 210 of the ORION-3 study, there was an average 51% reduction in LDL cholesterol and an average 77% reduction in PCSK9. In the ORION-3 study, a stable long-term LDL-lowering effect of a 300 mg dose of inclisiran was observed over approximately 22 months and the mean LDL reduction over time was approximately 60 mg/dL. No changes in the safety profile and laboratory tests of liver and kidney function were observed for at least 3 years. The most common adverse events with inclisiran therapy were nasopharyngitis (19%) and injection site adverse reaction (14%).

ORION-4 is a double-blind, randomized clinical trial that aims to study the effects of inclisiran and the clinical outcome of patients with cardiovascular disease. Approximately 15,000 patients aged ≥55 years were randomized 1:1 to receive inclisiran 300 mg or placebo (subcutaneously every 3 months and every 6 months) for a median follow-up of 5 years. Patients include the following criteria: previous ischemic stroke, peripheral vascular disease, or myocardial infarction. The ORION-4 trial will provide evidence of the effectiveness of inclisiran on major reversible cardiovascular events and overall prognosis in patients with CAD over one year. The results of the study are expected until 2026.[1,33]

ORION-5 was a study of 60 patients with homozygous familial hypercholesterolaemia in North America, Europe and the Middle East. Their primary endpoint was the percent change in LDL cholesterol at day 510 and the percent time-adjusted change between days 90 and 540 (ORION -9), as well as an analysis of the change in LDL level during treatment (ORION -5).[10,33] Responses are pending from the ongoing multinational trials ORION -4 and ORION -5, which evaluate the effect of inclisiran on cardiovascular outcomes in adults with established atherosclerotic cardiovascular disease and homozygous familial hypercholesterolaemia.[26,33]

The phase I study, ORION-7, evaluated the pharmacokinetics, safety, and tolerability of inclisiran in participants with renal impairment. All 31 participants were randomized 1:1:1:1 according to renal function (normal ≥ 90 ml/min; mildly impaired 60–89 ml/min; moderately impaired 30–59 ml/min; severely impaired 15–29 ml/min). min) to receive a single subcutaneous dose of inclisiran

300mg. Participants were followed until day 60, with an extended follow-up period of 180 days. Multiple pharmacokinetic endpoints included the relationship between the degree of renal impairment and the maximum plasma drug concentration (Cmax) of inclisiran, area under the curve (AUC) 0-infinity, and plasma half-life. The percentage change in LDL levels from baseline was assessed at 4 and 48 hours, and on days 4, 7, 30, 60, 120, and 180.[26,34]

The ORION-8 study examined the effect of inclisiran in patients at high risk of cardiovascular complications: «In the largest and longest follow-up to date with >12 000 patient-years exposure, inclisiran demonstrated consistent and effective LDL-C lowering with a favourable long-term safety and tolerability profile. Treatment-emergent adverse events at injection site (all mild/moderate) occurred in 5.9% of the patients. Inclisiran-associated anti-drug antibodies were infrequent (5.5%) and had no impact on the efficacy or safety of inclisiran. No new safety signals were identified. The hypothesis about the effect of the drug on the electrophysiological characteristics of the myocardium was also tested on healthy volunteers, but such an effect was not registered (ORION-12)».[31]

ORION-9 is an 18-month, multicenter, double-blind, randomized clinical trial (RCT) of 482 patients with heterozygous familial hypercholesterolaemia (FHC) treated with statins and ezetimibe. The average age of the patients was 55 years. At day 510, there was a 48% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -54% to -42%, $p < 0.0001$). By day 510, 52.5% of patients with ASCVD in the inclisiran group achieved a target LDL level of <1.8 mmol/L (70 mg/dL) compared to 1.4% with placebo. LDL <2.mmol/(100mg/dL) reached 66.9% of patients in the inclisiran group compared to 8.9% placebo.

ORION-10 is a multicentre, double-blind, month-long RCT involving 1561 patients with associated cardiovascular diseases (ASCVD). The average age of patients is 66 years. At day 510, there was a 52% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -56% to -49%, $p < 0.0001$). By day 510, 84% of patients in the inclisiran group achieved the target LDL level <1.8 mmol/L (70 mg/dL) compared to 18% with placebo.

ORION-11 is a multicentre, month-long, double-blind, RCT of 1617 patients with ASCVD risk equivalents. The average age of patients is 65 years. At day 510, there was a 50% reduction in LDL cholesterol percentage from baseline compared with placebo (95% CI, -53% to -47%, $p < 0.0001$). By day 510, 82% of patients with ASCVD in the inclisiran group achieved a target LDL level of <1.8 mmol/L (70 mg/dL) compared to 16% with placebo. LDL <2.mmol/(100mg/dL) reached 78% of patients in the inclisiran group compared to 31% with placebo.[31]

The ORION-14 study, includes 308 patients from a Chinese population, aimed to evaluate the pharmacokinetics and pharmacodynamics of inclisiran in patients with coronary artery disease or at high risk of developing it in patients with familial hypercholesterolaemia when prescribed maximum tolerated doses of statins. Inclisiran was generally safe and well tolerated. The greatest reductions were observed with the 300 mg regimen of Inclisiran.

The ORION-15 study: Inclisiran sodium 100, 200, and 300 mg demonstrated clinically meaningful and statistically significant LDL-C and PCSK9 reductions at Day 180, which were consistent over 12 months. Inclisiran was effective and well tolerated in Japanese patients with high cardiovascular risk with hypercholesterolaemia, including heterozygous familial hypercholesterolaemia.

In a placebo-controlled, multinational, phase III study, ORION-13 and ORION-16 are recruiting adolescents 12 to 17 years of age with homozygous and heterozygous familial hypercholesterolaemia and high LDL levels on stable lipid-lowering therapy to evaluate the short-term effectiveness of inclisiran.[31,35]

Further study of the effect of inclisiran in hetero-homozygous forms of familial hypercholesterolaemia will be continued in the planned studies ORION-19 (among homozygotes) and ORION-20 (among heterozygotes).[31,35]

Effect of PCSK-9 inhibitors and inclisiran on platelet function. The PCSK9-REACT study presents an associated association between PCSK9 and platelet activity in patients with acute coronary syndrome receiving dual antiplatelet therapy (DAPT). High levels of PCSK9 were associated with high platelet reactivity ($p=0.004$) and decreased effectiveness of antiplatelet drugs. Moreover, the results of this study showed a strong association between major adverse cardiovascular events and high levels of PCSK9.[7,36] The main limitations of in vivo studies are the combined use of statins and antiplatelet agents.

Wang et al assessed the relationship between PCSK9 and platelet reactivity in vitro to exclude the influence of other drugs (statins and antiplatelet agents) on the results. Subsequently, an in vivo study in healthy subjects without statins and antiplatelet drugs found that subjects with high levels of PCSK9 had higher platelet reactivity.[7] Frankie et al assessed the effect of evolocumab on platelet reactivity. Low LDL cholesterol levels were achieved at 30 days in all patients receiving evolocumab. Although evolocumab was associated with a statistically significant reduction in platelet reactivity units in the first 14 days, there was no change in platelet reactivity units (PRU) compared with placebo after 30 days ($p = 0.161$).[36]

The production of PCSK9 and Ox-LDL is increased in patients with hypercholesterolemia. High levels of PCSK9 in the blood activate platelet receptors CD36, which induce platelet activation through SRK and JNK kinases involved in the mechanism of thromboxane A2 production. PCSK9 increases ROC production by activating NOX2 on the platelet surface. This increases the formation of Ox-LDL, which enhances platelet activation through binding to CD36 and LOX1 receptors. This triggers platelet aggregation and thrombogenesis through the expression of p-selectin, CD40L and release of granules. PCSK9 inhibitors help reduce the activation of NOX2, CD36 and LOX1. Specifically, they demonstrated a reduction in oxidative stress by reducing

NOX2. In addition, a decrease in platelet aggregation is associated with a decrease in circulating platelet factors (thromboxane, PAF-4, CD62, CD40L and p-selectin), which was observed after 6 months of treatment.[7,37,38]

The ORION-1 study showed that the drug does not cause immunogenicity in relation to platelets, cells of the immune system (lymphocytes and monocytes) and immune markers (IL-6 and TNF-α).[7,39] PCSK9 protein is involved in proinflammatory and prothrombotic effects. In addition, high levels of PCSK9 enhance platelet aggregation.

Thus, an indirect, mediated effect of inclisiran on platelets is possible. Inclisiran, due to its highly specific hepatic absorption, acts only at the hepatic level. Consequently, inclisiran has no direct effect on PCSK9, which is present in other tissues such as intestinal cells, pancreatic cells, adipocytes, kidneys and brain.[7,40]

DISCUSSION

High residual platelet reactivity (HRPR) is a significant predictor of adverse cardiovascular outcomes, including myocardial infarction and stent thrombosis, particularly in patients with coronary artery disease. This underscores the importance of managing platelet aggregation and LCL-C levels to mitigate the progression of atherosclerosis. Elevated platelet aggregation is believed to enhance smooth muscle cell proliferation and foam cell formation, which contributes to atherogenesis by promoting LDL-C accumulation within atherosclerotic plaques.

Numerous studies highlight the interrelationship between lipid levels and platelet function. Specifically, elevated LDL-C levels have been shown to activate platelet aggregation, primarily through the binding of apolipoprotein B-100 to LDL receptors on platelets, resulting in altered signaling pathways and increased platelet sensitivity to stimuli. Higher mean platelet volume (MPV) has also been linked to an increased risk of ischemic events and thrombosis, suggesting that platelet volume indices are valuable markers in assessing cardiovascular risk.

According to the SCORE scale, which stratifies patients based on their 10-year risk of cardiovascular events, effective management of LDL-C levels is crucial, especially for individuals categorized as high, very high, or extreme risk. The European Heart Association emphasizes the importance of achieving target LDL-C levels—less than 1.8 mmol/L for high-risk patients and under 1 mmol/L for those at extreme risk. However, evidence indicates that a significant proportion of very high-risk patients fail to reach these targets, even with maximally tolerated statin therapy. This highlights the need for additional therapeutic strategies.

Recent advancements in lipid-lowering therapies, including the combination of statins with ezetimibe and the incorporation of monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab, show promising results in reducing LDL-C levels substantially. For instance, trials have demonstrated that evolocumab can lower LDL-C levels by approximately 60% and significantly decrease major cardiovascular events.

Bempedoic acid (BA) and inclisiran are emerging as novel agents with distinct mechanisms of action in LDL-C reduction. BA inhibits adenosine triphosphate (ATP) citrate lyase, leading to reduced LDL levels by up to 30% with monotherapy and 50% in combination with ezetimibe. Inclisiran employs RNA interference to decrease PCSK9 levels, enhancing LDL receptor recycling in hepatocytes and facilitating LDL uptake. Clinical trials have shown inclisiran to significantly reduce LDL-C levels and associated cardiovascular events, further establishing its role in managing dyslipidemia.

The relationship between PCSK9 and platelet reactivity is an area of ongoing investigation. Studies suggest that elevated PCSK9 levels are associated with increased platelet reactivity, potentially leading to worse cardiovascular outcomes. While PCSK9 inhibitors have shown promise in reducing oxidative stress and platelet aggregation, further research is necessary to delineate their direct effects on platelet function.

Overall, the collective evidence underscores the multifaceted nature of cardiovascular disease management, necessitating a comprehensive approach that includes aggressive lipid-lowering strategies and careful monitoring of platelet function. The integration of newer therapies, such as inclisiran and PCSK9 inhibitors, may play a critical role in achieving optimal outcomes for patients at high cardiovascular risk.

CONCLUSION

Most studies indicate the ineffectiveness of high-intensity statins in patients at high and extreme SCORE risk. Despite combination therapy with statins and ezetimibe or monoclonal antibodies, target LDL-C levels are not achieved in some cases. In addition, long-term therapy with statins, ezetimibe and monoclonal antibodies can lead to the development of side effects such as fibromyalgia and increased liver enzymes.

Inclisiran is the latest technology to lower LDL-C and PCSK-9 levels. From the above data, it is known that high LDL-C promotes increased platelet aggregation and the development of high platelet reactivity. Moreover, high levels of PCSK-9 protein are associated with high platelet reactivity in patients with CAD despite antiplatelet therapy. Inclisiran acts intracellularly, unlike monoclonal antibodies, reducing the production of the PCSK-9 protein and the uptake of LDL-C from the circulatory system. Since there is an association between high levels of PCSK-9, LDL-C and high platelet reactivity, it can be assumed that reducing PCSK-9 and LDL-C with inclisiran will help reduce platelet aggregation and reduce the incidence of cardiovascular complications in the long term. Thus, inclisiran represents a promising strategy for optimizing lipid control and reducing platelet activity in patients at high risk for cardiovascular diseases.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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An overview of hyperacute stroke services and National Stroke Registry in Malaysia - Improving stroke care through evidence

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ABSTRACT

Introduction: Stroke is a leading cause of death and disability in Malaysia. This paper provides an overview of the stroke burden, hyperacute stroke services, importance, and challenges of stroke registries. It also details findings from the National Stroke Registry (NSR) Malaysia that have advanced knowledge on local patterns, inequalities and temporal trends in stroke presentation, care processes and outcomes.

Materials and Methods: A recent survey that involved all the government (Ministry of Health, MOH) and university hospitals in Malaysia was conducted by a group of neurologists and researchers to provide insights into the hyperacute stroke services in Malaysia from 2012 to 2023.

Results: The results from the survey found that out of 142 MOH hospitals, 29 (20%) hospitals offer only intravenous thrombolysis (IVT) service, and seven (5%) hospitals offer both IVT and mechanical thrombectomy (MT) services. The majority or two-thirds of MOH hospitals still offer office hour services for both IVT and MT. For university hospitals, four (67%) out of six university hospitals provide both IVT and MT services and one (16%) university hospital provides only IVT service. Most university hospitals offer 24-hour services for IVT and MT. The availability of IVT service across MOH hospitals has increased significantly from 2012 to 2023. Thus, there was a substantial increase in the number of IVT cases treated in MOH hospitals. The growth in MT service has been more gradual. Only 22% of the MOH hospitals that provide hyperacute stroke services are equipped with acute stroke unit (ASU). Whereas ASU is available in 80% of the university hospitals that offer hyperacute stroke services. The higher availability of ASU in university hospitals compared to MOH hospitals may be due to better resources, specialised expertise, and advanced facilities in the university hospitals. The National Stroke Registry (NSR) Malaysia was established in 2009 to monitor stroke management practices, patient outcomes and promote quality improvement initiatives.

Conclusion: Despite suboptimal adherence on several key performance indicators, the NSR reports recent improvements in thrombolysis rates, reduced mortality, and better functional outcomes. Key recommendations center on promoting greater participation, feedback systems, adequate funding, and governance structures to translate registry findings into national policies and targeted interventions for equitable access to quality stroke care.

KEYWORDS:
National Stroke Registry Malaysia, stroke burden, hyperacute stroke services, intravenous thrombolysis, mechanical thrombectomy

INTRODUCTION

Globally, stroke ranks among the top three causes of disability-adjusted life years (DALYs) lost. In Malaysia, age-standardized stroke mortality rates per 100,000 population have worsened from 74 in 2010 to 105 in 2016 based on NSR reports.[1] As stroke often causes long-term disability, improvements across the continuum of care from prevention to rehabilitation are vital. Clinical registries like National Stroke Registry (NSR) play an invaluable role in monitoring stroke care quality, identifying gaps and generating evidence to inform policy and quality initiatives. This paper provides an overview of NSR Malaysia in terms of rationale, scope, research output and limitations. Potential recommendations to optimize NSR's utility as a national platform for quality evaluation and improvement are also discussed.

Stroke Burden and Services in Malaysia

As per Institute for Health Metrics and Evaluation estimates, in 2019 stroke was the third leading cause of death in Malaysia after ischemic heart disease and lower respiratory infection.[2] Analysis of administrative data on hospital admissions showed increased stroke incidence from 2008 to 2016, especially among those below 65 years (50% increase for men aged 35-39 years and 53% for women).[3] While 28-day all-cause stroke mortality has declined, the ratio of one

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death for every five strokes in women and one death for six strokes in men underscores room for improving acute care and secondary prevention.[3]

Information on dedicated stroke units was lacking. According to the information available on the My Stroke Hospital webpage, there are 69 stroke-ready hospitals identified, but details on their capabilities to definitively manage acute strokes were unavailable.[4] Therefore, a recent survey with the title of "An Overview of The Hyperacute Stroke Services in Malaysia from Year 2012 to 2023" was conducted by a group of neurologists and researchers from Seberang Jaya Hospital in 2024. This survey included a total of 142 government [Ministry of Health (MOH)] hospitals and six university hospitals to provide insights into the trend of both intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) services in Malaysia in terms of the total number of hospitals that provide IVT and MT services, the total number of hospitals that provide 24-hour IVT and MT services, the total number of hospitals equipped with acute stroke unit (ASU) and the total number of IVT and MT cases throughout the years from 2012 to 2023.

The survey [NMRR ID-24-00730-TKM (IIR)] has granted ethical approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia. The required data from each hospital was collected through an online questionnaire. A Google link that contained the questionnaire was shared with the neurologist or the main person in charge of stroke care in each hospital through email. The questionnaire consists of four different sections. Section one is about the respondent's details (name, designation, participating hospital). Section two and three consist of several questions pertaining to the IVT and MT services provided by each hospital respectively. While section four assesses the availability of ASU facility in the hospital. This survey has potential limitations. All the data captured was based on the feedback provided by the respondent of each hospital which was unverifiable. Ideally, the source of data should be from the national database which is the NSR Malaysia. Unfortunately, the number of hospitals that contribute data to the NSR is limited.

Intravenous Thrombolysis and Mechanical Thrombectomy Services Availability

As of March 2024, there are 142 government (MOH) and six university hospitals in Malaysia. Figure 1 shows the total number and percentage of MOH and university hospitals with IVT and MT services. Based on the information available from 142 government hospitals in Malaysia, 29 (20%) hospitals offer only IVT service and seven (5%) hospitals offer both IVT and MT services. Among six university hospitals, one (16%) hospital offers only IVT service, and four (67%) hospitals offer both IVT and MT services.

Figure 2 presents data on the total number of MOH hospitals that provide IVT and MT services from 2012 to 2023. The availability of both IVT and MT services across MOH hospitals has increased over the past decade. There was a significant increase in the number of hospitals providing IVT services between 2018 (6 hospitals) and 2023 (37 hospitals), indicating a substantial expansion of IVT service during that period. While the growth in MT service has been more gradual, there was a noticeable increase from one hospital in 2020 to seven hospitals in 2022, suggesting a recent focus on expanding MT services as well.

24-hour Service Availability

Table I shows the total number and percentage of MOH and university hospitals that offer 24-hour MT and/or IVT services. The majority or two-thirds of the MOH hospitals still offer office hour services for both IVT and MT. Most university hospitals offer 24-hour services for IVT and MT.

Acute Stroke Unit (ASU) Availability

Table II shows the total number and percentage of MOH and university hospitals that provide hyperacute stroke services equipped with ASU. The higher availability of ASU in university hospitals compared to MOH hospitals may be due to better resources, specialised expertise, and advanced facilities in university hospitals.

Service Utilization Trends

Figure 3 shows the total number of IVT and MT cases in MOH hospitals from year 2012 to 2023. The number of IVT cases treated in MOH hospitals has increased over the years, with a significant rise from 2018 onwards, reaching 916 cases in 2023. Similarly, MT cases in MOH hospitals have risen from 0 cases before 2016 to 72 cases in 2023.

Figure 4 shows the total number of IVT and MT cases in university hospitals from year 2012 to 2023. University hospitals have also seen a steady increase in IVT cases, from 16 in 2012 to 181 in 2023, and MT cases from zero before 2018 to 73 in 2023.

Overall, the findings indicate a positive trend in the expansion of the hyperacute ischemic stroke treatment services in Malaysia, with more hospitals adopting IVT and MT capabilities over the years. However, there are still significant gaps in service availability, particularly in terms of 24-hour service coverage and the presence of dedicated ASUs. The data also reveals regional disparities, suggesting the need for more equitable distribution of these critical services across the country.

Role of Stroke Registries

Clinical registries collect observational data on demographics, processes of care and outcomes to evaluate real-world practice against guidelines. They inform quality improvement initiatives, research and policies aimed at reducing evidence-practice gaps and unwanted variations in care quality. Stroke registries specifically enable monitoring of case volumes, treatment rates and adherence to certain key performance metrics. They benchmark hospital performance, while shedding light on inequalities in outcomes and longitudinal trends at regional and national levels.

For instance, the Clinical Research Collaboration for Stroke in Korea (CRCS-K) registry has been very helpful and beneficial for improving stroke care in Korea.[5] It has enabled the monitoring of secular trends in stroke epidemiology, quality indicators, and outcomes over time. This was associated with improved outcomes like reduced stroke recurrence, mortality,

Table I: The total number and percentage of MOH and university hospitals that provide 24-hour MT and/or IVT services

Type of hospital	Total number of hospitals that provide MT or IVT service n (%)	Total number of hospitals that provide MT or IVT service during office hours n (%)	Total number of hospitals that provide 24-hour MT or IVT service n (%)
MOH hospitals			
IVT service	36 (100.0)	23 (64.0)	13 (36.0)
MT service	7 (100.0)	5 (71.0)	2 (29.0)
University hospitals			
IVT service	5 (100.0)	1 (20.0)	4 (80.0)
MT service	4 (100.0)	1 (25.0)	3 (75.0)

Table II : The total number and percentage of MOH and university hospitals that provide hyperacute stroke services equipped with ASU

Type of hospital	Total number of hospitals that provide hyperacute stroke services n (%)	Total number of hospitals with no ASU available n (%)	Total number of hospitals with ASU available n (%)
MOH hospitals	36 (100.0)	28 (78.0)	8 (22.0)
University hospitals	5 (100.0)	1 (20.0)	4 (80.0)

Table III: Availability of hyperacute stroke treatment services in different states throughout Malaysia

State	Total number of MOH and university hospitals n	Total number of hospitals that offer only IVT service n	Total number of hospitals that offer both IVT and MT n
Perlis	1	0	0
Kedah	10	2	1
Pulau Pinang	6	2	0
Perak	14	4	0
Selangor	16	3	2
Wilayah Persekutuan Kuala Lumpur	3	0	3
Wilayah Persekutuan Putrajaya	1	0	0
Negeri Sembilan	7	2	0
Melaka	3	1	0
Johor	12	0	1
Pahang	12	2	0
Kelantan	10	3	1
Terengganu	6	1	0
Sabah	23	3	2
Wilayah Persekutuan Labuan	1	0	0
Sarawak	23	7	1
Total	148	30	11

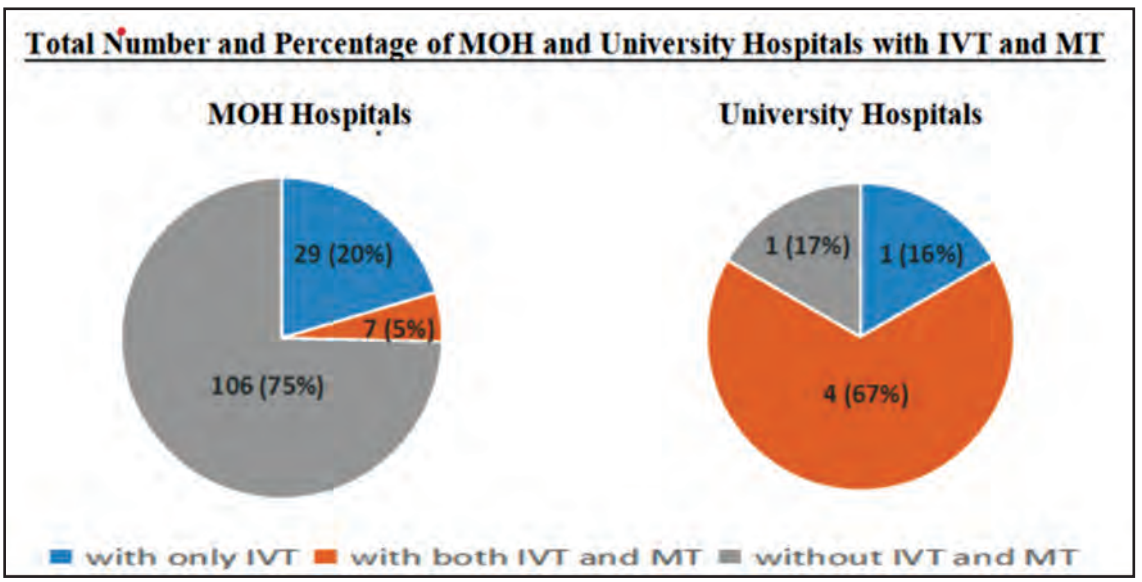

Fig. 1: The total number and percentage of MOH and university hospitals with IVT and MT services

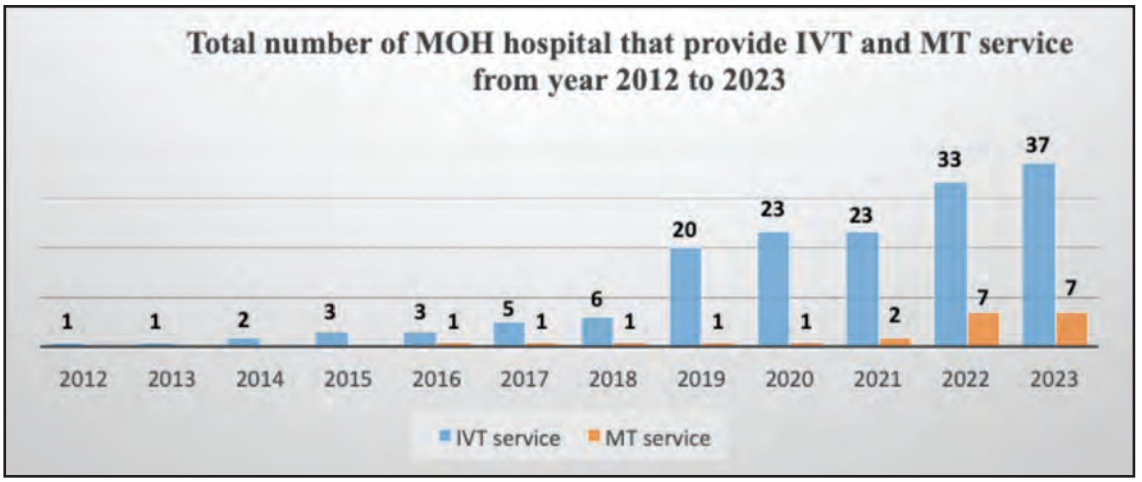

Fig. 2: The total number of MOH hospitals providing IVT and MT services from year 2012 to 2023.

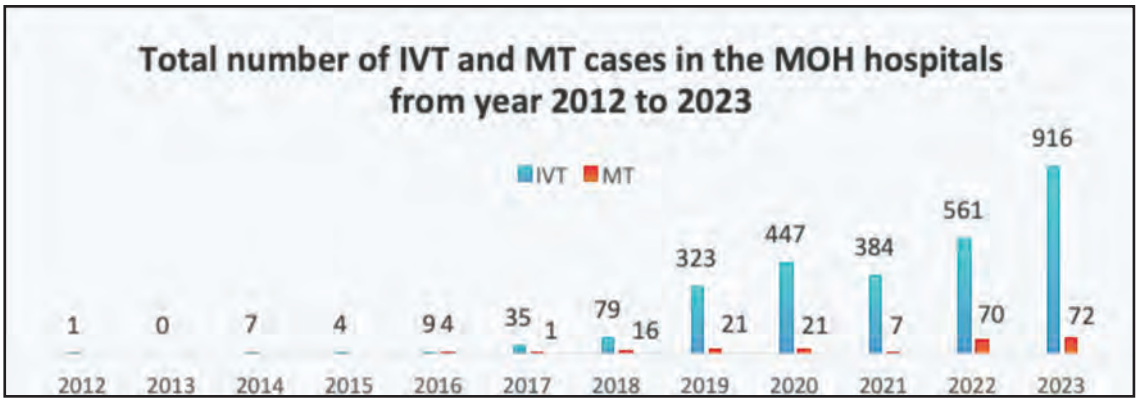

Fig. 3: Total number of IVT and MT cases in MOH hospitals from year 2012 to 2023

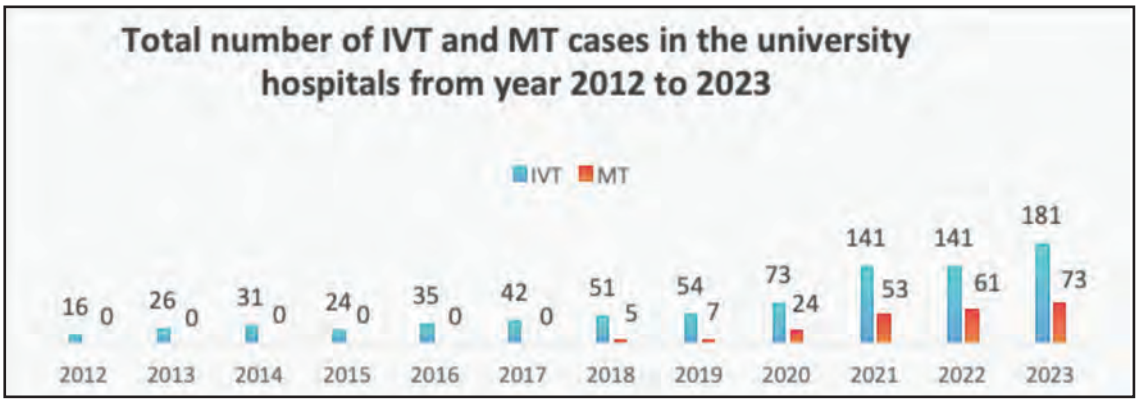

Fig. 4: Total number of IVT and MT cases in university hospitals from year 2012 to 2023

and better functional status. The large, high-quality dataset of about 100,000 registered stroke cases across 17 centres has enabled comparative effectiveness research studies comparing different treatment strategies that are difficult to study in randomised trials. Linkage of the registry data with other data sources has opened new research opportunities. International collaborations comparing the Korean dataset with other large stroke databases globally have enabled understanding of differences in stroke risk factors, aetiology, and outcomes across populations. Overall, the multicentre, prospective CRCS-K stroke registry has served as an invaluable resource for stroke epidemiology, comparative effectiveness research, clinical trials, and ultimately improving the quality of stroke care and outcomes in Korea over the past 15 years.

Over 1994-2013, 28 countries established population-based or hospital stroke registries with an additional seven more registries mainly from high income countries identified in 2017, but cross-national comparisons were limited by

inconsistent definitions and suboptimal coverage.[6-7] Recently, the Registry of Stroke Care Quality (RES-Q) was launched enabling international benchmarking across 103 countries through a common dataset.[8] Malaysia is one of the countries participating in RES-Q. A total of 35 hospitals within Malaysia have registered with a total of >9000 patients enrolled till 2023.[8] Locally adapted large-scale sustained registries can generate generalizable findings to advance stroke prevention and care.

NSR in Malaysia

The NSR was initiated in 2009 by the MOH, Malaysia as part of the National Neurology Registry to monitor practices, promote evidence-based care and identify areas for improvement nationally.[1] By capturing data from consenting patients older than 12 years with stroke onset within the last two weeks, it enables examining real-world outcomes. Participation is voluntary, but open to all public and private hospitals managing strokes. Patients are followed up for three months. Through December 2016, NSR accumulated details on 11,284 stroke hospitalizations from 15 sites.[1] The findings have been disseminated in publications, national meetings, and clinical practice guidelines.

Impact of NSR on Advancing Stroke Care in Malaysia

NSR studies have enhanced understanding of risk factor profiles, quality gaps and prognosis among the local stroke population. Appendix 1 summarizes major research findings from publications using data derived from the NSR Malaysia. Synthesizing results across these studies highlights progress made and continuing challenges in improving stroke care.

Delays in Care

Multiple studies have used the registry data to investigate prehospital delays in acute stroke treatment. Approximately 75% of patients had delayed hospital arrival more than 3 hours after symptom onset.[9] Contributing factors included milder stroke symptoms, ignorance, and use of private transport.[1,9,10] Public education campaigns stressing the need to seek urgent care even for mild stroke symptoms could help reduce onset-to-door times. In-hospital delays from door-to-imaging have also been examined. The median time to CT scanning was 4 hours, with only one third of ischaemic stroke patients being scanned within 4.5 hours.[11] Prioritization scores have been proposed to triage patients for urgent CT imaging when capacity is limited.[11]

Adherence to Guidelines

Registry data has revealed suboptimal adherence to clinical guidelines. Only 39% of patients with atrial fibrillation (AF) received anticoagulation and 39% received venous thromboembolism (VTE) prophylaxis.[12] Prescription of antihypertensives for secondary prevention was around 50%.[13] The main areas of suboptimal key performance indicator (KPI) adherence (non adherence rate >25%) were deep vein thrombosis (DVT) prophylaxis (82.8%), anticoagulation for AF patients (49.8%), and rehabilitation (26.2%).[14] Non-adherence to performance measures was linked to higher mortality.[14] Quality improvement efforts must continue to increase evidence-based prevention and treatment.

Risk Factors and Recurrence

Ischemic heart disease has been identified as an independent predictor of recurrent stroke, especially in patients with diabetes.[15,16] Elevated triglycerides were also associated with recurrence.[17] Targeting modifiable vascular risk factors is key for secondary stroke prevention. One study developed a predictive model for recurrence based on risk factor profiles.[18]

Outcomes

Encouraging trends in reduced mortality and improved functional independence at hospital discharge have been observed from 2009 to 2017.[19] However, thrombolysis rates remain low at around 20%, signaling room for improvement in hyperacute management.[20]

The NSR Malaysia has enabled important research characterizing stroke epidemiology, treatments, outcomes and prognostic factors. Key findings include opportunities to enhance preventive care and reduce delays. Mortality has declined but functional recovery remains poor for many patients. Continued commitment to translating registry insights into clinical improvements is critical for optimal stroke care delivery and outcomes.

Limitations and Recommendations for the National Stroke Registry (NSR) Malaysia

Limitations:

- Data entry can be impractical, especially for district hospitals, due to the comprehensive nature of the NSR and its wide range of parameters.
- Certain parameters captured in the RES-Q are absent in the current NSR, resulting in redundant data entry for hospital staffs participating in both systems. Appendix 2 summarizes the comparison between NSR Malaysia and RES-Q Registry parameters.
- Lack of motivation and sustainability in maintaining the registry due to insufficient dedicated manpower, inconsistent encouragement, and monitoring.
- Many staff members remain unaware of the registry's importance, hindering its effectiveness.
- Concerns regarding data privacy persist, necessitating vigilant oversight in registry maintenance efforts.

Recommendations:

- Implementation of a new NSR project, which is currently in progress, to address these limitations. The goals of the new NSR project include:

i. Demonstrate progress in stroke care through data analysis.
ii. Identify gaps and areas lacking comprehensive data by harmonising the current NSR and RES-Q and ensuring the inclusion of necessary national KPIs.
iii. Introduce a simplified, user-friendly version of the stroke registry to facilitate efficient data collection and encourage wider participation from healthcare facilities.
iv. Advocate for dedicated funding and resources by highlighting the significance and potential benefits of a coordinated NSR.
v. Enable detailed data analysis to inform evidence-based decision-making, drive quality improvement initiatives, and enhance the overall quality of stroke care nationwide.

Additional Recommendations:

- Appoint Stroke Champions in every state, with possible expansion to district hospitals where feasible, to improve monitoring and encouragement for stroke registry data submission. The Stroke Champion is a neurologist or physician identified to lead stroke services in each state. This role involves serving as a mediator between the state and various stakeholders, including the MOH Malaysia. The Stroke Champion is also the primary contact for stroke data in the state and may be responsible for conducting training and audits to improve stroke care.
- Encourage participation in the Stroke Preceptorship Programme among young and dynamic neurologist fellows, who would collaborate closely with selected district hospital medical department heads for training and registry/audits.
- Emphasize the importance of stroke registries during regular stroke workshops.
- Establish awards like the Stroke Rising Stars and Angels Awards to recognize outstanding performances among stroke champions and incentivize participation in the stroke registry. For example, World Stroke Organization (WSO) partners with ANGELS initiative do give out WSO Angels Awards quarterly to recognize and promote best practice in stroke care. There are three different levels for WSO Angels Awards which are "Gold Status", "Platinum Status" and "Diamond Status". The award level achieved will depend on the data captured by the hospital in the last three months.
- Mandate registry participation with adequate reimbursements and data manager support.
- Implement governance policies ensuring rigorous privacy protections and access oversight.
- Secure funding for ongoing development, analyses, and feedback systems.
- Develop practical web-interfaces, dynamic data checks, and interactive visualizations.
- Provide training modules on interpreting reports and applying findings for audits and practice improvement.
- Engage stakeholders through multidisciplinary expert panels to formulate and track progress on registry-informed quality targets.

CONCLUSION

Despite limitations, Malaysia's concerted efforts towards establishing the NSR have helped uncover management and prognosis patterns, inequalities among subgroups and temporal shifts. This has paved the pathway for enlightened policies and programs to alleviate the stroke burden through equitable access to quality evidence-based services. With continued strive towards a well-governed, adequately funded national registry with widespread participation, Malaysia is well poised to lead transformations in regional stroke care.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ETHICAL APPROVAL

Ethical approval for the survey [NMRR ID-24-00730-TKM (IIR)] was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia prior to the conduct of the research. Approval from the Director General of Health Malaysia was granted for manuscript publication.

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Appendix 1: Key Research Findings from Publications Using Malaysian NSR Data

Study	Key Findings	Author, Year
National Stroke Registry (NSR): Terengganu and Seberang Jaya experience	- Only 38.6% received VTE prophylaxis - 39.4% with AF received anticoagulation	Nazifah et al., 2012[12]
Acute Stroke Registry Malaysia, 2010-2014: Results from the National Neurology Registry	- Incidence increased dramatically from 2010-2014 - Need for risk factor control to prevent further increase in stroke burden	Aziz et al., 2015[21]
Factors associated with delay in seeking treatment by patients with acute stroke: The National Neurology Registry (NNeuR) of Malaysia	- 75.7% had delayed arrival (>3 hrs) - Patients with mild/moderate stroke had longer delays than severe stroke	Neelamegam et al., 2015[9]
Clinical characteristics of atrial fibrillation in first-ever ischaemic stroke patients; results from Malaysia National Neurology Registry	- AF associated with more severe stroke, poorer outcomes and higher mortality	Aziz et al., 2016[22]
Gender disparities and thrombolysis use among patient with first-ever ischaemic stroke in Malaysia	- Females older at stroke onset, had more severe strokes, poorer outcomes - Lower thrombolysis rates in females	Aziz et al., 2016[23]
Use of a diagnostic score to prioritize Computed Tomographic (CT) Imaging for patients suspected of ischaemic stroke who may benefit from thrombolytic therapy	- Only 33% of the ischemic stroke patients had CT imaging within 4.5 hours - The median door-to-scan time was 4 hours - Proposed Siriraj Stroke Score to prioritize CT imaging for ischaemic stroke	Hwong et al., 2016[11]
Use of antihypertensive drugs and ischaemic stroke severity - is there a role for angiotensin-ii?	- No difference in stroke severity between Angiotensin II vs Angiotensin II suppressors	Hwong et al., 2016[24]
Annual report of the Malaysian Stroke Registry 2009-2016	- Median time from symptom onset to hospital arrival was 7.6 hours. - Only 21% arrived within 3 hours of onset - Common reasons for delay: ignorance about symptoms, mild symptoms, geographical barriers - Overall mortality increased from 74 to 105 per 100,000 from 2010 to 2016 - 35% were independent (MRS 0-2), 54% disabled (MRS 3-5), 11% died by discharge - Poor adherence to VTE prophylaxis and anticoagulation guidelines	Available from: https://www.neuro.org.my[1]
Prescription of secondary preventive drugs after ischaemic stroke: results from the Malaysian National Stroke Registry	- <50% prescribed antihypertensives and 1/3 prescribed anticoagulants	Hwong et al., 2017[13]
Gender differences and risk factors of recurrent stroke in Type 2 Diabetic Malaysian population with history of stroke: the observation from Malaysian National Neurology Registry	- Ischaemic heart disease significantly associated with recurrence in both males and females	Aziz et al., 2019[15]
Trends in stroke outcomes at hospital discharge in first-ever stroke patients: Observations from the Malaysia National Stroke Registry (2009-2017)	- Improved functional outcomes from 2009 to 2017 - Decreased mortality over time	Chen et al., 2019[19]
A hospital-based study on ischaemic stroke characteristics, management, and outcomes in Sarawak: Where do we stand?	- 18.8% thrombolysis rate - 57% good functional outcomes at discharge - High Get With The Guidelines (GWTG) - Stroke compliance	King et al., 2020[20]
Impact of adherence to key performance indicators on mortality among patients managed for ischaemic stroke	- The main areas of suboptimal KPI adherence (nonadherence rate >25%) were DVT prophylaxis (82.8%), anticoagulation for AF patients (49.8%), and rehabilitation (26.2%). - Suboptimal KPI adherence associated with higher mortality	Mohammed et al., 2020[14]
Modelling the prognostic effect of glucose and lipid profiles on stroke recurrence in Malaysia: an event-history analysis	- Triglycerides consistently associated with stroke recurrence	Chen et al., 2020[17]

Appendix 1: Key Research Findings from publications using Malaysian NSR data

Study	Key Findings	Author, Year
Predictors of recurrent ischemic stroke in obese patients with Type 2 Diabetes Mellitus: a population-based study	- Ischaemic heart disease, hypertension, antihypertensives associated with recurrence in obese patients with type 2 diabetes mellitus	Albitar et al., 2020[25]
Socio-demographics and clinical characteristics affecting pre-hospital delays in acute stroke patients: A 6-year registry study from a Malaysian stroke hospital	- Shorter delays in Chinese patients and ambulance users - Longer delays with lacunar infarcts	Loh et al., 2020[10]
Population-based study comparing predictors of ischaemic stroke recurrence after index ischaemic stroke in non-elderly adults with or without diabetes	- Ischaemic heart disease main predictor regardless of diabetes status	Elhefnawy et al., 2021[16]
Predictive model of recurrent ischaemic stroke: model development from real-world data	- 4.32% had recurrent stroke within 7 years - Model predicted hazard over time and with risk factors	Elhefnawy et al., 2023[18]
Antiplatelet therapy for secondary prevention in patients with ischaemic stroke and transient ischaemic attack: a retrospective cohort study in Malaysia	- DAPT reduced risk of stroke, myocardial infarction, or death compared to SAPT at 1-year follow-up (hazard ratio 0.48, 95% CI 0.25-0.91). - DAPT reduced risk of recurrent stroke compared to SAPT at 1 year (hazard ratio 0.38, 95% CI 0.16-0.92)	Rahman et al, 2024[26]

Appendix 2: Comparison between NSR Malaysia and RES-Q Registry Parameters

This table compares the unique parameters captured in each stroke registry system. Parameters that are common to both systems are not shown. Understanding these differences helps to explain why healthcare providers need to enter data twice when participating in both systems.

Category	NSR Only	RES-Q Only
Demographics	Ethnicity	None
Stroke Presentation	None	• Wake-up stroke status • From where patient arrived to the hospital (home/ another stroke treating centre/ any other hospital)
Medical History	None	• Congestive cardiac failure • Hormone therapy • HIV infection • COVID-19
Initial Assessment	None	• Baseline Modified Rankin Scale (mRS) prior to stroke
Brain Imaging	None	• ASPECT score • Previous infarct detection • Blood vessel occlusion on Computed Tomography Angiography (CTA) / Magnetic Resonance Angiography (MRA)
Treatment Details	None	• Reasons for not performing: - Intravenous thrombolysis (IVT) - Mechanical thrombectomy (MT)
Post Acute Care	None	• Fever (equal or more than 37.5) in the first 72 hours of admission • Glucose level of equal or more than 10mmol/L in the first 48 hours of admission
Hospital Stay Information	• Length of stay	• None

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