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

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

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Clinical and radiological outcomes of SARS-CoV-2 related organising pneumonia in COVID-19 survivors

Sze Shyang Kho, MD[1,2], Kah Chuan Lim, MD[3], Noorul Afidza Muhammad, MD[1], Mona Zaria Nasaruddin, MD[1], Izyan Ismail, MMed (Rad)[4], Ummi Nadira Daut, MD[1,5], Jamalul Azizi Abdul Rahaman, MBBChBAO[1]

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ABSTRACT

Introduction: COVID-19 patients frequently demonstrate radiological organising pneumonia (OP) pattern. The long-term outcome and treatment options for this group of patients remain uncertain. We aim to describe the clinical and radiological outcomes of patients with COVID-19-related OP and identify possible clinical factors associated with inferior radiological outcome.

Materials and Methods: Post-COVID-19 clinic attendees, consisting of post-COVID-19 patients discharged from major hospitals in the state of Selangor during the third pandemic wave of COVID-19 in Malaysia, were enrolled in this retrospective study for 6 months. Physician-scored Modified Medical Research Council (mMRC), patient self-reported quality of life (EQ-VAS) score and follow-up CT scan were evaluated.

Results: Our cohort comprised 131 patients, with a median age of 52 (IQR 39–60) years and median BMI of 29.40 (IQR 25.59–34.72). Majority (72.5%) had co-morbidities, and 97.7% had severe disease requiring supplementary oxygen support during the acute COVID-19 episode. 56.5% required intensive care; among which one-third were invasively ventilated. Median equivalent dose of methylprednisolone prescribed was 2.60 (IQR 1.29–5.18) mg/kg during admission, while the median prednisolone dose upon discharge was 0.64 (IQR 0.51–0.78) mg/kg. It was tapered over a median of 8.0 (IQR 5.8–9.0) weeks. Upon follow-up at 11 (IQR 8–15) weeks, one-third of patients remained symptomatic, with cough, fatigue and dyspnoea being the most reported symptoms. mMRC and EQ-VAS scores improved significantly (p<0.001) during follow-up. Repeat CT scans were done in 59.5% of patients, with 94.8% of them demonstrating improvement. In fact, 51.7% had complete radiological resolution. Intensive care admission and mechanical ventilation are among the factors which were associated with poorer radiological outcomes, p<0.05.

Conclusion: Approximately one-third of patients with SARS-CoV-2-related OP remained symptomatic at 3 months of follow-up. Majority demonstrated favourable radiological outcomes at 5-month reassessment, except those who required intensive care unit admission and mechanical ventilation.

KEYWORDS:
COVID-19, SARS-CoV-2, post-COVID-19, organising pneumonia, Malaysia

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged as a novel coronavirus in 2019. It soon spread globally to cause an unprecedented Coronavirus Disease 19 (COVID-19) pandemic in human history.[1] Malaysia was not spared from this global outbreak. To date, we had experienced four major waves of COVID-19, with 4.6 million reported cases in total,and overall mortality rate of 0.77%.[2]

A significant number of COVID-19 patients develop severe disease characterised by progressive respiratory failure with features similar to acute respiratory distress syndrome (ARDS).[3] ARDS carries high mortality risk and complicates around 33.0–41.8% of COVID-19 patients.[4,5] Cytokine storm is frequently seen in this group of patients as SARS-CoV-2 could trigger a state of dysregulated and excessive proinflammatory cytokines release, which in turn result in widespread multiorgan failures.[6] Radiologically, they frequently demonstrate radiographic features that are compatible with organising pneumonia (OP).[7] OP is a distinct clinicopathological entity characterised by peripherally and basally distributed bronchocentric and perilobular patterns of consolidation. Histologically, organisation and proliferation of granulation tissue buds within distal airspaces of the lungs are frequently described.[8] Historically, OP demonstrates a dramatic response to prolonged high doses of corticosteroid with favourable outcomes.[8] Therefore, high-dose, prolonged corticosteroid therapy was believed to be potentially an important therapeutic player in SARS-CoV-2-related OP during the early phase of the pandemic.Case reports and series had demonstrated promising outcomes with the usage of cortico steroid therapy in this group of patients.[9] This was also in line with our national guideline recommendations,of which high-dose potent corticosteroid was recommended for patients with severe COVID-19 diseases.[10]

In this study, we aim to assess the clinical and radiological outcomes of SARS-CoV-2-related OP during their follow-up

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visit after being discharged from acute COVID-19 admission. In addition, we aim to assess differences in clinical parameters between patients with favourable and undesirable radiological outcomes.

MATERIALS AND METHODS

Design and Participants

A retrospective chart review of post-COVID-19 clinic attendees between February 2021 to August 2021 (6 months duration) in Serdang Hospital, Malaysia, was carried out. A dedicated post-COVID-19 clinic was established in Serdang Hospital during the early phase of COVID-19 pandemic to cater to the need for follow-up for post-COVID-19 patients from the state of Selangor. Our centre received referrals from major hospitals in the state of Selangor as we remained the only hospital equipped with interstitial lung disease services in the state. The study was approved by the Medical Research & Ethics Committee, Ministry of Health Malaysia *(NMRR-ID-22-01910-NSB-IIR, dated 14th September 2022*).

All post-COVID-19 clinic attendees aged 18 years and above during the study period, who were previously admitted for acute COVID-19 episode, were included in this study.Patients who were managed as outpatients during the acute COVID-19 episode, as well as those who defaulted the post-COVID-19 clinic follow-up, were excluded.

Data Collection

Clinical Variables

Baseline demographic characteristics,including age, gender, height, weight, body mass index (BMI), smoking history, and comorbidities were collected. In addition, clinical data regarding COVID-19 admission(oxygen requirement, length of hospital stay, intensive care admission, mechanical ventilation, CT scan findings, and steroid therapy details) were obtained from referral letters and/or electronic medical records.

Physician Scored Dyspnoea Score

Modified Medical Research Council (mMRC) dyspnoea scale was assessed and scored by the managing physician during follow-up. mMRC scale is as follows: 0, dyspnoea only on strenuous exercise; 1, dyspnoea when hurrying or walking up a slight hill; 2, dyspnoea when walking on level ground with people of same age or at own pace on the level; 3, dyspnoea after 100 meters or walking after a few minutes on level ground; 4, dyspnoea to even leave the house or dressing. In addition to current dyspnoea scale during clinic follow-up, patients were asked to recall and assessed by the managing physician for patient's dyspnoea scale upon discharge from COVID-19 admission, and dyspnoea scale pre-COVID-19 admission, i.e., their baseline premorbid status before COVID-19 infection.

Patient Scored Quality of Life Scale

EuroQOL EQ-5D-3L visual analogue scale (EQ-VAS) was used to assess patient's self-reported quality of life (QoL). EQ-VAS is a vertical visual scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). It is used as a quantitative health outcome measurement reflecting patient's own judgement. Patients were instructed to score their current EQ-VAS score during the follow-up, as well as to recall their EQ-VAS score upon discharge from COVID-19 admission and pre-COVID-19 admission, i.e., their premorbid status before COVID-19 infection.

Outcomes of Computed Tomography Thorax

All post-COVID-19 clinic attendees were evaluated by the managing physician. A repeat computed tomography of thorax in high-resolution construction (HRCT) would be scheduled if the initial COVID-19 admission imaging showed features consistent with SARS-CoV-2-related OP. HRCT thorax was obtained in supine position during deep inspiration and breath-holding. Acquired images were assessed and analysed by the in-house general and thoracic radiologists. HRCT reports uploaded into the Picture Archiving and Communication System (PACS) were reviewed and outcomes were recorded.

Statistical Analysis

Data analysis was performed using SPSS version 21 (Chicago, IL, USA).Descriptive statistics of the continuous variables with non-normal distribution were expressed in median and interquartile range (IQR) while continuous variables with normal distribution were expressed in mean and standard deviation. Group comparison was assessed using the Mann–Whitney U-test for continuous non-normally distributed data and t-test for normally distributed data.Chi-square or Fisher's exact test was used for categorical data where appropriate. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 131 patients were included in this study. They were admitted to the major hospitals in Selangor state for COVID pneumonia between November 2020 to April 2021, during which the SARS-CoV-2 variant B.1.524 predominated.[11]

Baseline Demographic Characteristics

Almost two-thirds of our cohort were male patients (58.8%),and the median age was 52 (IQR 39–60) years. The ethnic distribution followed the multi-racial population of Malaysia,of which Malay ethnicity comprised the majority at 78.6%. Median body mass index was 29.40 (IQR 25.59–34.72) kg/m^2, and 72.5% had co-morbidities. Half of the cohort were diabetic (51.9%) and hypertensive (50.4%). The detailed baseline demographic characteristics were presented in Table I.

Baseline COVID-19 Admission Characteristics

Majority (97.7%) of patients required supplementary oxygen during their admission. Median length of hospital stay was 12.50 (IQR 9.00–17.00) days, among which 56.5% required intensive care admission and one-third required invasive positive pressure ventilation for a median of 4.5 (IQR 3.0–9.0) days. All patients had computed tomography evidence of OP, and 42.7% had evidence of concurrent pulmonary embolism. During admission, intravenous methylprednisolone was given at a median equivalent dose of 2.60 (IQR 1.29–5.18) mg/kg/day. Oral prednisolone was prescribed at a median dose of 0.64 (IQR 0.51–0.78) mg/kg/day upon discharge and tapered over 8.00 (IQR 5.85–9.00) weeks (Table I).

Table I: Baseline demographic and COVID-19 admission characteristics

Number of patients, n		131
Gender, n (%)	Male	77 (58.8)
	Female	54 (41.2)
Median age, years (IQR)		52 (39-60)
Ethnicity, n (%)	Malay	103 (78.6)
	Chinese	19 (14.5)
	Indian	7 (5.3)
	Indigenous	2 (1.6)
Smoking, n (%)	Current smoker	5 (3.8)
	Ex-smoker	47 (35.9)
	Never smoker	79 (60.3)
Median body mass index, kg/m2 (IQR)		29.40 (25.59-34.72)
Presence of co-morbidities, n (%)		95 (72.5)
Co-morbidity, n (%)	Diabetes mellitus	68 (51.9)
	Essential hypertension	66 (50.4)
	Dyslipidaemia	33 (25.2)
	Ischemic heart disease	15 (11.5)
	Chronic kidney disease	7 (5.3)
	Asthma and COPD	8 (6.1)
	Malignancy	1 (0.8)
Disease Severity, n (%)	Not requiring oxygen	3 (2.3)
	Requiring supplementary oxygen	128 (97.7)
Admission, n (%)	General ward	57 (43.5)
	Intensive care unit	74 (56.5)
Median admission duration, days (IQR)		12.50 (9.00-17.00)
Highest oxygen requirement, n (%)	Room air	3 (2.3)
	Nasal cannula	28 (21.4)
	Face mask	29 (22.1)
	High-flow nasal cannula	30 (22.9)
	Invasive positive pressure ventilation	41 (31.3)
Median invasive ventilation duration, days (IQR)		4.5 (3.0–9.0)
CT evidence of organising pneumonia, n (%)		131 (100.0)
CT evidence of pulmonary embolism, n (%)		56 (42.7)
Median dose of methylprednisolone given, mg/kg/day (IQR)		2.60 (1.29–5.18)
Median dose of prednisolone prescribed upon discharge, mg/kg/day (IQR)		0.64 (0.51–0.78)
Median prednisolone tapering duration upon discharge, weeks (IQR)		8.00 (5.85–9.00)

CT=computed tomography, IQR= interquartile range.

Table II: Clinical and radiological outcomes of post-COVID-19 patients during follow-up

Persistent symptoms during follow-up, n (%)		47 (35.9)
Symptoms, n (%)	Dyspnoea	21 (16.0)
	Fatigue	18 (13.7)
	Cough	13 (9.9)
	Myalgia	10 (7.6)
	Non-specific chest pain	8 (6.1)
	Rhinitis	6 (4.6)
	Headache	6 (4.6)
	Sore throat	3 (2.3)
	Dry mouth	3 (2.3)
Median mMRC, score (IQR)	Baseline (pre-COVID-19)	0 (0-1)
	Upon discharge	2 (1-3)
	During follow-up	1 (0-2)
Median EQ-VAS, score (IQR)	Baseline (pre-COVID-19)	95.0 (80.0–100.0)
	Upon discharge	60.0 (45.0–70.0)
	During follow-up	80.0 (75.0–90.0)
Repeat HRCT thorax available, n (%)		78 (59.5)
HRCT thorax outcome, n (%)	Complete resolution	42 (53.8)
	Residual changes	33 (42.3)
	Fibrotic	3 (3.8)

HRCT: high resolution computed tomography, IQR: interquartile range, mMRC: modified Medical Research Council, EQ-VAS: EuroQol Visual Analogue Scale

Table III: Differences between patients with complete resolution and with residual changes on repeated high resolution computed tomography (HRCT) thorax assessment (n=78)

	Complete Resolution	Residual Changes	*p*-value
Median age, years (IQR)	50.0 (36.0–60.0)	55.0 (42.0–63.5)	0.285
Male gender, n (%)	21 (48.8)	22 (51.2)	0.325
Current or ex-smoker, n (%)	18 (56.3)	14 (43.8)	0.722
Median BMI, kg/m2 (IQR)	30.6 (25.8–37.5)	27.9 (24.7–30.8)	0.025
Supplementary oxygen during COVID-19 admission, n (%)	40 (52.6)	36 (47.4)	0.185
Intensive care unit admission, n (%)	19 (41.3)	27 (58.7)	0.008
Invasive ventilation, n (%)	10 (34.5)	19 (65.5)	0.008
Median dose of methylprednisolone given, mg/kg/day (IQR)	2.01 (0.78–3.53)	4.85 (1.82–6.41)	0.003
Median dose of prednisolone prescribed upon discharge, mg/kg/day (IQR)	0.62 (0.47–0.78)	0.70 (0.58–0.81)	0.051
Median prednisolone tapering duration upon discharge, weeks (IQR)	6.00 (5.00–8.00)	8.00 (7.00–9.00)	0.026
Interval of HRCT thorax scans, weeks (IQR)	24.0 (13.8–32.0)	19.0 (15.0-26.0)	0.330
mMRC during follow-up, score (IQR)	1.00 (0.00–1.25)	1.00 (0.00–1.75)	0.987
EuroQOL during follow-up, score (IQR)	80.0 (73.7–90.0)	82.5 (71.2–90.0)	0.771

BMI: Body mass Index, IQR: Interquartile range, HRCT: High-resolution computed tomography, mMRC: Modified Medical Research Council

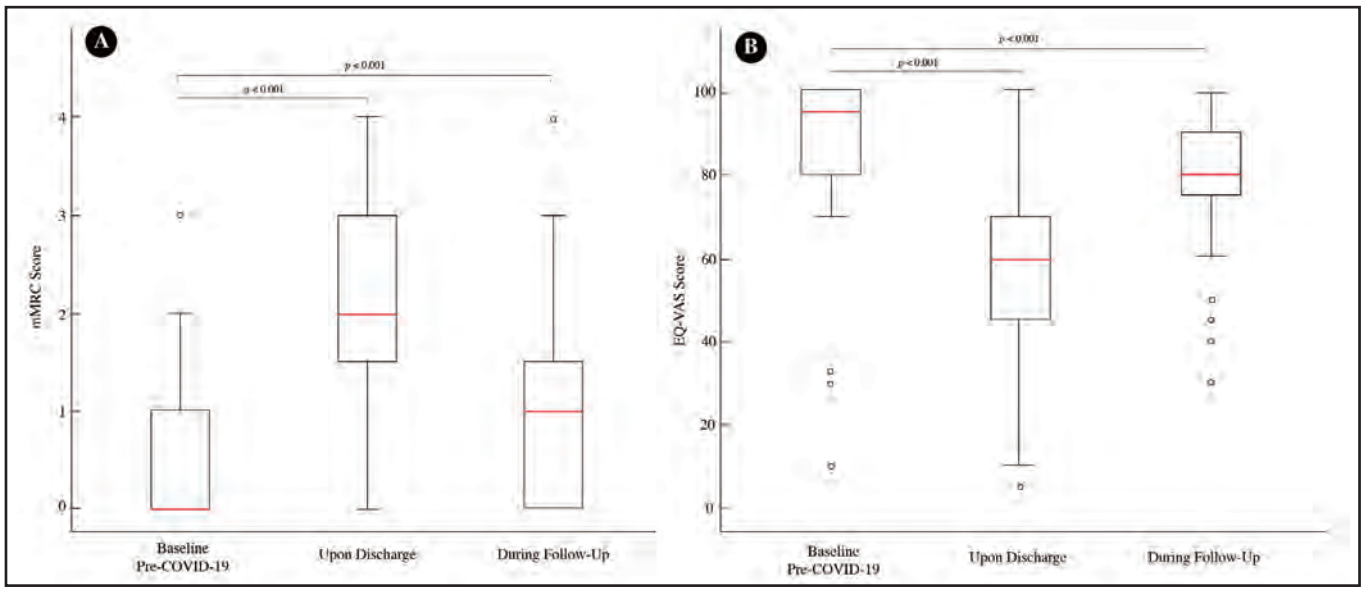

Fig. 1: Boxplot showing dyspnoea mMRC score (Panel A) and quality of life EQ-VAS score (Panel B) during baseline pre-COVID-19, upon discharge, and follow-up

Clinical Outcomes of Post-COVID-19 Patients During Follow-up

Patients were seen at post-COVID-19 follow-up clinic at a median of 11 weeks (IQR 8–15) post-discharge. Almost one-third (35.9%) of patients reported persistent symptoms during follow-up. The commonest symptom reported was dyspnoea (16.0%), followed by fatigue (13.7%) and cough (9.9%). Other symptoms include myalgia, non-specific chest pain, rhinitis, headache, sore throat, and dry mouth (Table II). Median mMRC score during follow-up was 1 (IQR 0–2) while median EQ-VAS score was 80.0 (IQR 75.0–90.0). These were significantly improved compared to patients' scores upon discharge (p<0.001),but did not return to patients' baseline pre-COVID-19 scores (p<0.001), as summarised in Figure 1.

Radiological Outcomes of Post-COVID-19 Patients During Follow-up

In our cohort, 78 patients (59.5%) had repeat HRCT thorax during follow-up. Repeat HRCT thorax was done at a median of 21.0 (IQR 15.0–30.5) weeks from the first admission CT. Majority (96.1%) of patients had significant radiological

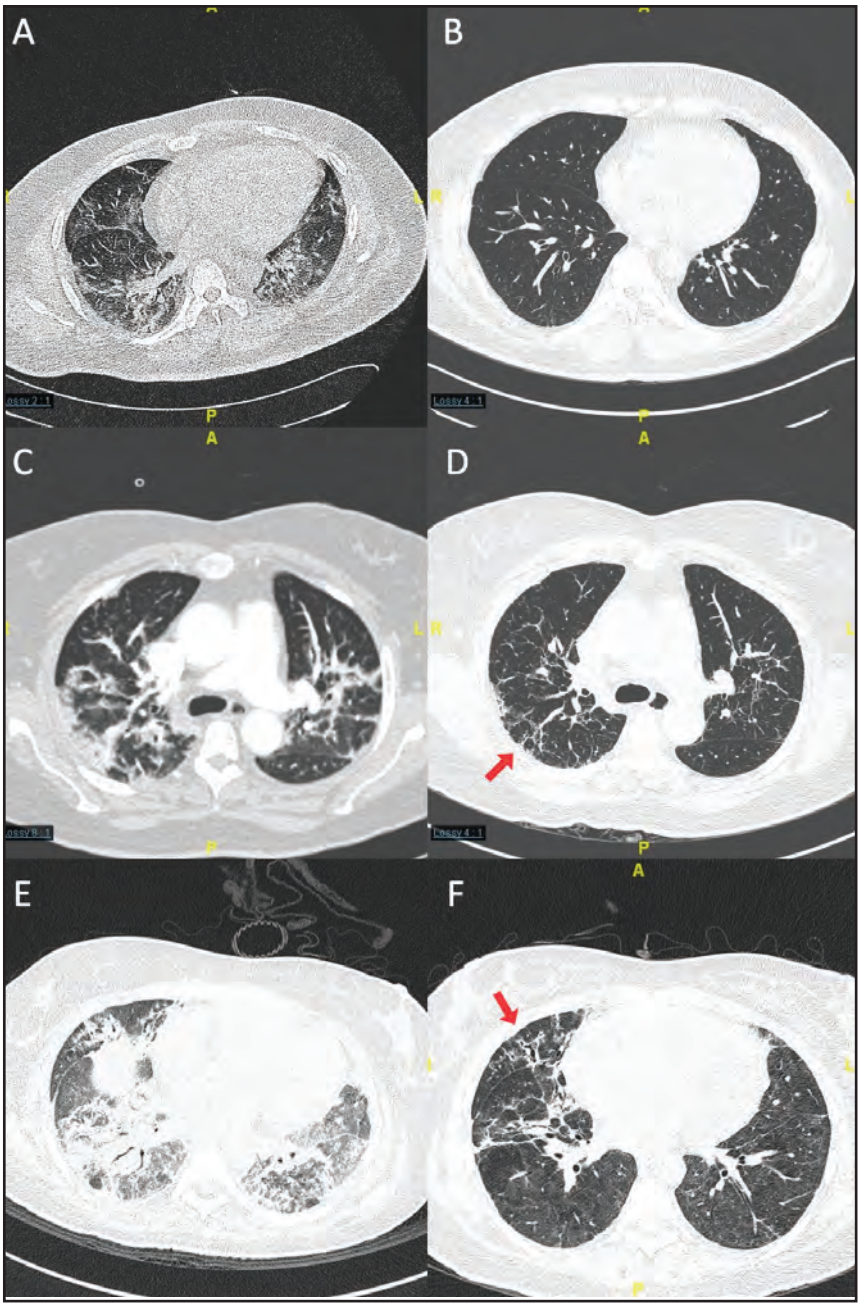

Fig. 2: Representative Cases.

Case 1 (Complete Resolution) – 49 years old lady with type 2 diabetes mellitus and hypertension presented with severe COVID-19 pneumonia required invasive ventilation (Panel A); patient was treated with intravenous methylprednisolone followed by tapering dose of oral prednisolone over 6 weeks at a dose of 0.54mg/kg/day, repeated CT scan three months later shown complete resolution of initial changes with improvement of mMRC and EQ-VAS score (Panel B).

Case 2 (Residual Changes) – 60 years old lady without chronic medical illness was admitted to intensive care for severe COVID-19 pneumonia requiring high flow nasal cannula oxygen therapy (Panel C); she was treated with intravenous methylprednisolone followed by tapering oral prednisolone at a dose of 0.57mg/kg/day over 4 weeks, repeated CT scan 4 months later shown residual peripheral reticulation (arrow, Panel D) with improvement of mMRC and EQ-VAS score from 3 to 1 and 40 to 90 respectively.

Case 3 (Fibrotic Complication) – 25 years old lady with type 1 diabetes mellitus and Grave's disease presented with severe COVID-19 pneumonia (Panel E) required prolonged ventilation and tracheostomy which was complicated with nosocomial multi-resistant Acinetobacter baumannii pneumonia. She was treated with intravenous methylprednisolone and tocilizumab followed by a tapering dose of oral prednisolone over 8 weeks at a dose of 1mg/kg/day; she improved at 4 months follow up with improvement of mMRC and EQ-VAS score but repeated CT shown focal traction bronchiectasis at the non-dependent area (arrow, Panel F) consistent with post-ARDS and infective changes.

improvement, of which half (53.8%) of them demonstrated complete resolution of COVID-19 changes, while 33 (42.3%) patients had residual radiological changes, and 3 (3.8%) had fibrotic changes on their repeat CT scans (Figure 2, Table II).

Among the 78 patients in whom the HRCT thorax was repeated, there were no significant differences in terms of median age, gender, and smoking status between patients with complete resolution and residual changes (Table III).

Interestingly, we found that patients with residual CT changes had lower median body mass index compared to those with complete resolution (27.9 vs. 30.6 kg/m^2, p<0.05). Patient who required intensive care admission and those who received invasive ventilation were also associated with residual changes on repeat CT, p<0.01. In contrast, supplementary oxygen requirement during admission was not associated with worse radiological outcomes.

Patients with residual CT changes received significantly higher equivalent dose of methylprednisolone (4.85 vs. 2.01 mg/kg/day, p<0.01) and was discharged with a longer duration of prednisolone tapering period (8.0 vs. 6.0 weeks, p<0.05). There was no statistical difference in prednisolone dose upon discharge, although patients with residual CT changes trend towards higher prednisolone dose. Interestingly, inferior radiological outcome was not associated with worse mMRC or EQ-VAS score in our cohort.

DISCUSSION

The World Health Organization declared COVID-19 as a global pandemic on 11th March 2020. SARS-CoV-2 is one of the deadliest pandemics in human history. Until July 2022, there were more than 569 million confirmed cases,with an overall death rate of around 1.12% worldwide.[12] Asian countries generally recorded a lower death rate attributed to younger generation, better adoption of facemask and physical distancing, as well as better preparedness from the previous SARS outbreak.[13] This lower mortality rate also translates to a huge number of COVID-19 survivors with distinct issues (long COVID-19 syndrome) which need to be addressed.[14] Although post-COVID-19 follow-up data on clinical and radiological outcomeshad been published at an immense speed in the global literature, local data from our region is still lacking. In this study, we presented the clinical and radiological outcome of SARS-CoV-2-related OP in Malaysia for the first time, which will aid clinicians in future decision-making.

For clinical outcomes, our study demonstrated that 35.9% of patients remain symptomatic at 11 weeks *(approximate to 3 months)* post-COVID-19. This is in concordance with several studies which have shown that a significant number of patients (16.3–45.9%) remain symptomatic at 3 months.[15-17] In our cohort, the most reported symptoms were dyspnoea, fatigue and cough, which wereconsistent withthose in other literatures.[16,17] In addition, our study evaluated specifically the physician-scored dyspnoea scale (mMRC) and patient self-reported quality of life scale (EQ-VAS), and our data indicate that most patients improved but had yet to return to their pre-COVID-19 baseline. For mMRC dyspnoea scale, we were in line with literature evidence that mMRC score was >0 in most of the patients at 3 months follow-up, however, reassuringly improved with times.[18,19] Our study is also in agreement with the literature that post-COVID-19 patients had perceived reduced quality of life at 3 months; 79.5% were due to respiratory symptoms.[20] Interestingly, we also support the findings from a previous study that dyspnoea and quality of life score were not associated with radiological outcomes.[20] This finding further strengthened the fact that long COVID-19 is a multi-factorial condition. Hence, a multidisciplinary approach to address this complex clinical problem is essential.[14]

Two-thirds of our patients had repeat HRCT thorax at around 21 weeks *(approximate to 5 months)* from their first admission scans. In concordance with the literature, majority of patients in our cohort showed significant improvement, among which half of them had complete radiological resolution. From the literature, the reported rates of residual radiological changes at 3–6 months post-COVID-19 were wide (19–82%). In our cohort, 42.3% had residual radiological changes. Reported factors associated with residual changes include advanced age, intensive care admission, and acute respiratory distress syndrome.[15,19-22] Again, this is consistent with our data. Wu et al. demonstrated good radiological outcomes in their cohort of patients; they were scanned at 3-monthly intervals up to 12 months and they showed patients continued to improveup to 9 months, but remained static thereafter.[18] Reassuringly, all residual changes were non-progressive in nature in their study.[18] Although three patients were reported as having fibrotic features in our cohort, further analysis revealed that two of the patients were having mild *non-progressive* traction bronchiolectasis with subpleural parenchymal band likely secondary to post-infective changes, while another one was having post ARDS and infective changes after suffering from concurrent multi-drug-resistant *Acinetobacter* pneumonia during admission. Therefore, the fibrosis sequelae might not be directly related to SARS-CoV-2 infection. Another interesting observation in our study is that patients with residual HRCT changes had lower BMI than patients with complete resolution. A possible explanation is that obese patients were managed more aggressively during COVID-19 admission as it is a known risk factor for deterioration. This may translate to a better outcome due to aggressive management.[23] Nevertheless, we urge to interpret this data cautiously as anthropometric measurement may not always be optimal and accurate in a COVID-19 ward setting.

The survival benefit of steroid therapy was proven in RECOVERY Trial in which patients with SARS-CoV-2 infection requiring invasive mechanical ventilation and supplementary oxygen benefited from a 10-day course of dexamethasone at a dose of 6mg once daily.[24] OP is a radiological pattern frequently associated with severe SARS-CoV-2 infection. As OP, often seen in inflammatory interstitial lung disease, is usually corticosteroid-sensitive,the fear of progressive fibrotic OP in severe COVID-19 had led to the prescription of high dose and prolonged steroid during the early phase of the pandemic.[25-27] In our study, we demonstrated that favourable radiological resolution was not associated with higher methylprednisolone or prednisolone doses upon discharge. In fact, patients with residual

radiological changes were significantly associated with higher methylprednisolone dose and longer prednisolone tapering duration. This is very likely due to the prescription bias of the managing physician, as this group of patients was likely to have more severe diseases requiring higher oxygen supplementation and intensive care admission. A study from the United Kingdom also revealed that only a minority of patients would require rescue steroid therapy after radiological and physiological assessments at 6 weeks after discharge.[28] As more data have now emerged, SARS-CoV-2-related OP is generally associated with favourable outcomes with good recovery given time.[29] We truly believe that the usage of high dose steroid *(along with immunomodulator)* should only be reserved in severe COVID-19 patients during the acute phase in cytokine storm syndrome, as prolonged high dose steroid may lead to other potential complications, such as sepsis, gastrointestinal bleeding and uncontrolled diabetes mellitus.

LIMITATIONS

Our study is not without limitations. First, the single institution experience with retrospective design may not address the actual clinical and radiological outcomes. However, as patients were recruited from all major hospitals in the state of Selangor, we believe that our data remain useful for the clinicians regionally, as it represents a real-world experience. Second, our study is compounded by survival bias in which we only captured post-COVID-19 clinic attendees; patients who suffered mortality during admission, and those who were re-admitted to respective hospitals, as well as those who defaulted our clinic follow-up were not included. Hence, the high prevalence of patients with favourable radiological outcomes may be biased. Third, as the subjects were required to score their dyspnoea and quality of life score retrospectively for their general conditions upon discharge and pre-COVID-19 status, this practice was subject to recall bias. Forth, we did not describe the exact radiological patterns during follow-up scans, for example,ground glass opacity, traction bronchiectasis, degree of volume loss, but was only based solely on an overall qualitative radiological evaluation. Finally, since we only captured patients during SARS-CoV-2 B.1.524 variant-predominant COVID-19 period, during which the national COVID-19 immunisation program had just started, the clinical and radiological outcomes among vaccinated patients, as well as those infected with other SARS-CoV-2 variants, for example, Delta variant, B.1.617.2 and Omicron variant, B.1.1.529, in the subsequent waves of COVID-19 pandemic could never be ascertained.

CONCLUSION

Approximately one-third of SARS-CoV-2 patients with OP remained symptomatic at 3-month follow-up, with dyspnoea and quality of life scores improving significantly but did not return to baseline. Majority demonstrated favourable radiological outcomes at 5-month reassessment, but patients who required intensive care admission and mechanical ventilation were associated with inferior radiological outcomes.Interestingly, this inferior radiological outcome was not associated with worse dyspnoea and quality of life scores in our cohort.

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We would like to express our deepest gratitude to all healthcare workers and frontliners who have worked and contributed selflessly during this unprecedented COVID-19 pandemic.

DECLARATIONS

This study was approved by the medical research and ethics committee, Ministry of Health Malaysia (NMRR-ID-22-01910-NSB-IIR, dated 14th September 2022).

Availability of data and material The data that support the findings of this study are available from corresponding author (SSK) upon reasonable request.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

The authors declare that no funding was received for the publication of this study.

AUTHORS CONTRIBUTION

Conceptualisation: SSK, KCL, NAM, MZN, JAAR; data curation and formal analysis: KSS, NAM; Methodology: SSK, NAM, MZS, II; writing original draft: SSK, KCL, NAM; writing review and editing: KCL, NAM, II, UND, JAAR.

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Left main stem stenosis angioplasty with intravascular ultrasound optimisation criteria guidance using a new generation everolimus drug-eluting stent

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ABSTRACT

Introduction: Intravascular ultrasound (IVUS) is recommended in the use of left main stem (LMS) percutaneous coronary intervention (PCI). Since the LMS diameter is usually larger than other coronary arteries, a new generation everolimus drug-eluting stent (DES), Synergy Megatron DES (Boston Scientific) has better axial and radial strength allowing more post implant overexpansion and consequently better suited for LMS lesions. We performed a study to evaluate the clinical outcomes of PCI using 1) an improved IVUS protocol with optimisation targets and 2) the use of Megatron stents.

Materials and Methods: This was a study involving LMS PCI coronary lesions using the Synergy Megatron DES. An IVUS protocol using predefined optimisation targets to evaluate for stent malapposition, longitudinal stent deformation, optimal stent expansion >90% of reference lumen and appropriate distal landing zone was used in all cases. The primary end-point was procedural success, defined by successful stent implantation with <30% residual stenosis. The secondary end-point was in-hospital and 30-day major adverse cardiovascular event (MACE).

Results: Eight patients with significant LMS stenosis were successfully treated with the Megatron stent. The primary end-point was achieved in all patients. There were no cases of stent malapposition or longitudinal stent deformation, one case did not have optimal LMS stent expansion and one case did not have an appropriate distal landing zone. IVUS optimisation criteria were met in 6 (75%) cases. There were no complications of coronary dissection, slow or no reflow, stent thrombosis or vessel perforation. None of the patients suffered in-hospital or 30-day MACE. The average LMS MLD at baseline was 2.1 ± 0.1mm and the post-PCI LMS MLD was 4.0 ± 0.5mm, with a significant acute luminal gain of 1.9 ± 0.7mm (p<0.01). A post-PCI MSA of 17 ± 3.9 mm2 was numerically superior compared to those documented in other LMS PCI trials.

Conclusion: This study demonstrates low rates of short-term major adverse cardiovascular events among patients with LMS PCI using the Megatron stents. It highlights the usefulness of IVUS-guided optimisation in LMS PCI. With the use of intravascular imaging, the new generation stent technology can improve the treatment of large proximal vessels and PCI of LMS lesions.

INTRODUCTION

Left main stem (LMS) stenosis is often regarded as clinically significant since the LMS bifurcates to the left anterior descending and left circumflex vessels, providing blood supply up to two-thirds of the left ventricle.[1] Due to the importance of good clinical outcomes following LMS angioplasty, current European guidelines recommend the use of intravascular ultrasound (IVUS) in patients undergoing LMS percutaneous coronary intervention(PCI).[2] When IVUS is used to evaluate plaque morphology, lumen characteristics and optimise stent sizing, clinical outcomes can be improved.[3] IVUS also provides better imaging of the LMS ostium and is often considered the first-line imaging method for LMS stenosis.[4] Better visualisation and assessment during PCI to the LMS helps to avoid complications such as inadequate stent expansion and malapposition of stent struts.[5] Both stent underexpansion and malapposition of stent struts have been shown to be predictors of acute stent thrombosis and early stent restenosis.[6] More recently, IVUS optimisation criteria has been used specifically for LMS intervention with good clinical outcomes, and we sought to implement the use of such criteria to guide LMS PCI in our cases.[7]

Current stent technology is limited by the capability of stents to expand beyond a certain limit, and since LMS diameter is often of large calibre, newer stent technology can provide improvements to clinical outcomes. Use of post-dilation balloons that exceed the recommended upper size limit may risk damage to the stent integrity and lead to long-term complications for PCI. The Synergy Megatron drug-eluting stent (DES) platform (Boston Scientific) is a new generation everolimus-coated stent, which offers improved over expansion capabilities.[8] This is a new stent technology, with little available data on clinical outcomes with the use of the stent.

This study has two objectives: the first is to evaluate the use of IVUS optimisation criteria and second is to evaluate clinical outcomes using a new generation stent technology in the PCI of LMS lesions.

MATERIALS AND METHODS

Patients and Study Design

This was a retrospective single-centre study. Patients with PCI to the LMS using the Synergy Megatron DES were included.

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Data were collected by medical record review. Patients gave informed consent for the publication of images. Baseline characteristics of patients, including age, cardiac risk factors and clinical presentation, left ventricular ejection fraction (LVEF) and baseline renal function (eGFR), were documented.

PCI and Intravascular Imaging
All patients were given dual-antiplatelet therapy and received intra-venous heparin during the PCI procedure. IVUS was performed in all cases. Measurements of baseline mean luminal diameter (MLD) and mean luminal area (MLA) were done. The angioplasty balloon size was selected based on vessel diameter measured by IVUS at a 1:1 ratio. Non-compliant (NC) balloons were used in all cases for post-dilation of the LMS stent. IVUS was used post-PCI to assess procedural success and document post-procedural complications. Post-PCI measurement of MLD and minimal stent area (MSA) were done. Following PCI, all patients were given dual antiplatelet therapy with either aspirin 100 mg, clopidogrel 75mg, or ticagrelor 180 mg/day for 12 months.

PCI results were evaluated according to an IVUS optimisation criteria which had been previously used for LMS intervention.[7] There were four areas used to define procedural success by IVUS assessment (Figure 1):

1) *Complete stent apposition* was defined by the absence of any IVUS evidence of malapposition (separation of ≥1 stent strut from the intimal surface of the arterial wall).[9]
2) *Absence of longitudinal stent deformation (LSD),* where multiple layers of stent struts are seen in any single cross-section within a single stent.[10]
3) *Optimal LMS stent expansion* is defined as follows: expansion >90% of the distal reference lumen in ostial and mid-LMS lesions, as well as expansion >90% of the proximal reference lumen in distal LMS lesions.
4) *Appropriate distal landing zone* was defined as distal stent edge with residual plaque burden <40% and absence of edge dissection.[11]

Endpoints
The primary end-point was defined as successful stent implantation with <30% residual stenosis. The secondary endpoints were in-hospital major adverse cardiovascular event (MACE), including cardiac death, myocardial infarction (MI), or target-vessel revascularization (TVR) and 30-day MACE.[12] Safety outcomes were procedural complications, defined as coronary dissection, slow or no reflow, stent thrombus or vessel perforation. A target MSA of the LMS post-PCI was 8 mm^2.[13]

Statistical Analysis
Statistics including mean and percentages were used. Categorical variables are presented as counts (%) and continuous variables are presented as mean ± standard deviation. The paired t-test was used for the comparison of MLD at baseline and MSA after PCI. A *p*-value of ≤ 0.05 was considered significant.

RESULTS

Baseline Clinical and Procedural Characteristics
Between October 2021 and October 2022, eight patients had LMS PCI using the Megatron stent. The baseline characteristics of the patients are shown in Table I.

Procedural Characteristics
Of the eight LMS lesions treated, 3 (37.5%) were distal LMS stenosis (Table II). Femoral vascular access was preferred in the majority of cases. The average stent diameter was 3.7 ± 0.3 mm, and stent length was 24 ± 5.6 mm. The average post dilatation non-compliant (NC) balloon diameter used was 5 ± 0.3 mm. Pre- and post-PCI coronary angiogram for two of the cases are shown in Figure 2.

Clinical Outcomes
The primary endpoint of successful stent implantation was achieved in all patients. There were noin-hospital MACE and 30-day MACE events (Table II). There were no cases of coronary artery dissection, slow flow or stent thrombosis. There were no cases of stent malapposition or longitudinal stent deformation, 1 (12.5%) case did not have optimal LMS stent expansion and 1 (12.5%) case did not have an appropriate distal landing zone (Table II). IVUS optimisation criteria were met in 6 (75%) of the cases. The average LMS MLD at baseline was 2.1 ± 0.1mm and the post-PCI LMS MLD was 4.0 ± 0.5mm, with significant acute luminal gain of 1.9 ± 0.7mm (p<0.01). The post-PCI MSA was 17 ± 3.9 mm^2. All cases achieved the LMS target MSA of > 8mm^2.

DISCUSSION

The main findings of our study are as follows: 1) IVUS optimisation criteria help to guide effective LMS PCI. 2) New generation stent technology can improve expansion capabilities with a low complication rate in LMS PCI.

IVUS optimisation criteria in LMS Angioplasty
Angiographic assessment of the LMS can be difficult. Due to the two-dimensional nature of coronary angiography, there is limited evaluation of the extent of disease and vessel-wall characteristics.[14] The latest European Society of Cardiology guidelines indicate a class IIa recommendation for the use of IVUS in LMS PCI to overcome these limitations.[15,16] IVUS provides information on accurate vessel dimensions to ensure optimal stent sizing and balloon sizing used for post- stent dilation (i.e., proximal optimisation technique [POT]).[17] Evaluation of post-PCI IVUS should include assessment for stent malapposition, stent underexpansion, exclusion of longitudinal stent deformation and stent-edge dissection.[18] Due to the complexity of various IVUS criteria, the use ofI VUS with predefined optimisation targets has been associated with improved clinical outcomes.[19,20] We have used these criteria successfully in our study to guide effective PCI.

Stent under expansion is the main predictor of stent failure and is associated with higher rates of target lesion revascularization (TLR) and stent thrombosis. IVUS criteria to achieve 90% MSA in the stented segment of the average reference cross-sectional area is frequently recommended.[21] We observed 1 case (12.5%) which did not achieve 90% MSA within the stent segment, although it did not directly predispose to any acute complication. This is in keeping with a previous registry where 12% of cases did not achieve > 90% stent expansion.[20] A previous study examined optimal IVUSMSA values for preventing in-stent restenosis in the LMS.[13] The recommended values were 5.0mm^2 for the left circumflex (LCX) ostium, 6.3 mm^2 for the left anterior descending (LAD) ostium, 7.2 mm^2 for the distal LMS and 8.2 mm^2 for the proximal LMS.[13] Subsequently, the "5-6-7-8 Rule"

Table I: Baseline Characteristics

Male, n (%)	86 (100)
Age (mean ± SD)	55 ± 12
Hypertension, n (%)	5 (63)
Hypercholesterolaemia, n (%)	4 (50)
Smoking, n (%)	2 (25)
Family history of cardiac disease, n (%)	2 (25)
Diabetes mellitus, n (%)	2 (25)
LVEF (mean ± SD %)	58 ± 4
eGFR (ml/min/1.73 m^2)	77 ± 27
Stable angina/positive stress test	4 (50)
Unstable angina	4 (50)

LVEF: Left Ventricular Ejection Fraction
eGFR: Estimated Glomerular Filtration Rate

Table II: Procedural characteristics and clinical outcomes

Left main stem disease, n (%)	
Ostial LMS	0%
Distal LMS	3%
Diffuse LMS	1%
Ostial LAD	4%
Procedural characteristics	
Procedural time (min ± SD)	103 ± 14
Fluroscopytime (min ± SD)	25 ± 9
Femoral vascular access, n (%)	5 (62.5)
Radial vascular access, n (%)	3 (37.5)
Stent parameters	
Stent diameter (mm ± SD)	3.7 ± 0.3
Stent length (mm ± SD)	24 ± 5.6
LMS post-dilatation NC balloon, mm (mean ± SD)	5 ± 0.3
IVUS characteristics	
Baseline LMS MLD	2.1 ± 0.1
Post-PCI LMS MLD (mean ± SD)	4.0 ± 0.5
Baseline LMS MLA (mean ± SD)	4.5 ± 0.5
Post-PCI LMS MSA (mean ± SD)	17 ± 3.9
Post-PCI LMS Luminal Gain (mean ± SD)	1.9 ± 0.7
Failure to Achieve LMS Target MSA > 8mm^2	0
Achievement of IVUS optimisation criteria	
Stent malapposition, n (%)	0 (0)
Longitudinal stent deformation, n (%)	0 (0)
Optimal LMS stent expansion, n (%)	7 (87.5)
Inappropriate distal landing zone, n (%)	1 (12.5)
Angiographic and clinical outcomes	
Procedure success with facilitated stent delivery	8 (100)
Perforation, dissection, slow flow, stent thrombosis	0 (0)
In-hospital MACE (MI/TVR/Death)	0 (0)
30-Day MACE (MI/TVR/Death)	0 (0)

LMS: Left main stem
LAD: Left anterior descending
PCI: Percutaneous coronary intervention
MLD: Minimal luminal diameter
MLA: Minimal luminal area
MSA: Minimal stent area
IVUS: Intravascular ultrasound
MACE: Major adverse cardiovascular events
MI: Myocardial infarction
TVR: Target vessel revascularization

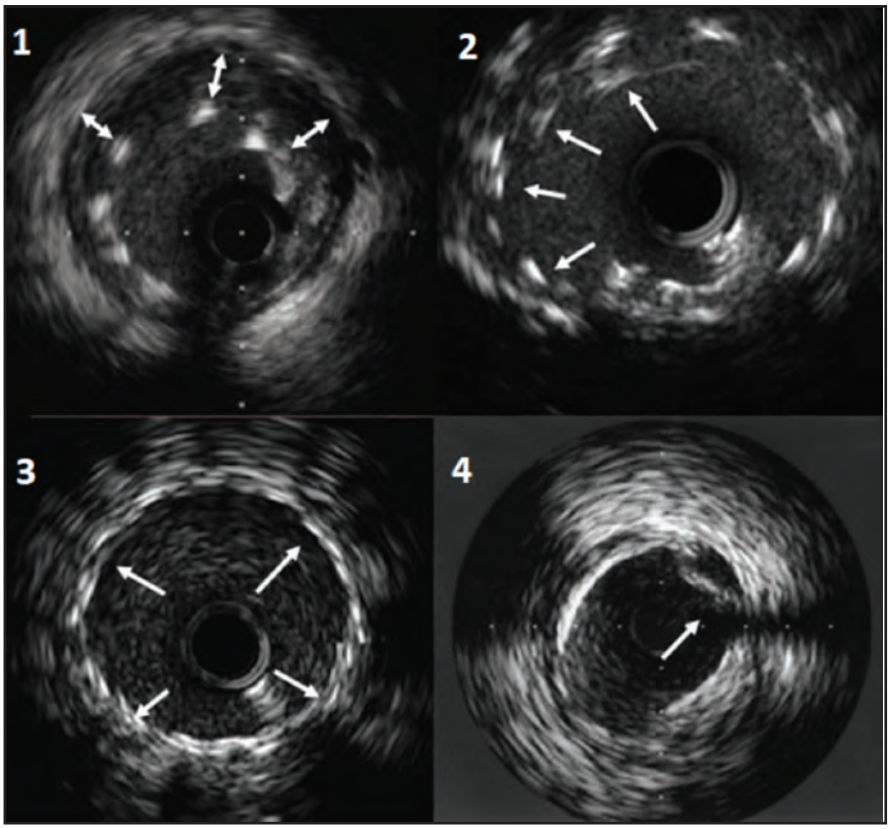

Fig. 1: Examples of IVUS images showing stent malapposition (1), longitudinal stent deformation (2),optimal LMS stent expansion (3), and stent edge dissection (4)

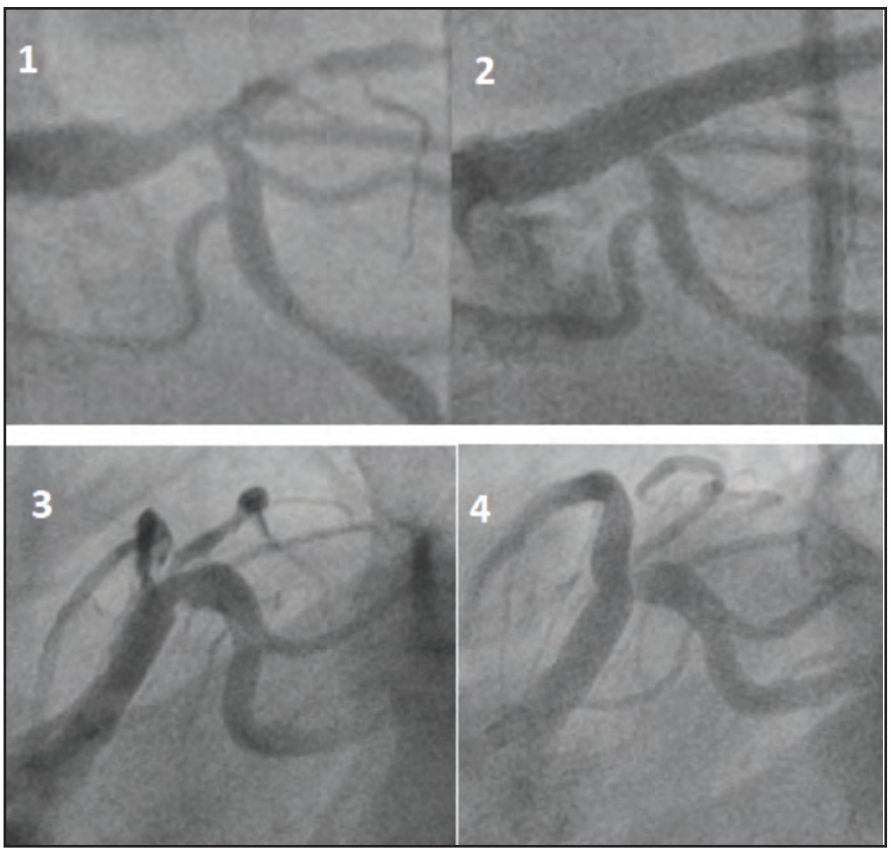

Fig. 2: Coronary angiogram of two cases. The first case shows severe distal LMS stenosis and proximal LAD stenosis (1). Post-PCI with the Megatron stent shows good results with no residual LMS or proximal LAD stenosis (2). The second case shows severe ostial LAD stenosis with a need to place the stent into the LMS (3). Post-PCI with the Megatron stent shows good results with no residual ostial LAD stenosis (4).

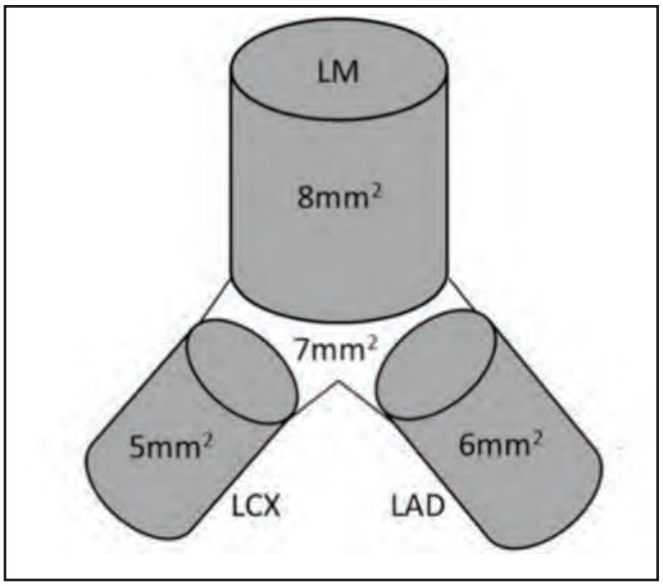

Fig. 3: Recommended MSA values for LMS, LAD and LCX arteries

was proposed on the basis of the minimum stent area (MSA) within each segment of the LMCA bifurcation (Figure 3). In our study, the recommended MSA value of > 8 mm^2 at the LMS above the polygon of confluence was achieved in all cases.

Stent malapposition is a lack of contact between at least one stent strut and the intimal surface of the artery. Significant malapposition often is seen on IVUS as stent struts floating in the lumen.[22] Stent edge dissection is also associated with increased complications of TLR[23] and early stent thrombosis.[24] Among our study cohort, there were no cases of stent malopposition or edge dissection. Appropriate distal landing zone with the stent landing on sites with plaque burden >40% appears increase the risk of subsequent stent edge restenosis.[25] In our cohort, 1 case (12.5%) did not achieve an appropriate distal landing zone as compared to a previous registry where 8% of the patient did not achieve this criteria.[20]

Longitudinal stent deformation occurs when multiple layers of stent struts are seen in any single cross-section image within a single stent. Acute deformation of second-generation DES has been seen in 8% of LMS PCIs. LSD of the stent is seen more frequently in LMS procedures.[26] The presence of stent deformation is associated with a significantly higher incidence of LMS-related acute coronary events and complications of TLR.[27]

Our study showed that it was frequently possible to meet IVUS optimisation targets using the Megatron DES stent technology for stent malapposition, stent expansion, appropriateness of landing zones, avoiding LSD and stent edge dissection.

A New-Generation Everolimus-Eluting Stent Platform

Previous experience with LMS PCI using older generation stents and infrequent use of intracoronary imaging guidance had demonstrated suboptimal outcomes for PCI when compared to CABG.[28] The majority of patients with LMS stenosis have a mean vessel diameter of >4 mm, suggesting the requirement for post-dilation beyond the nominal diameter of current generation DES devices in patients requiring LMS angioplasty.[29] Due to the large calibre of the left main artery, it may be difficult with older generation stents to achieve optimal MSA during LMS PCI. The Megatron DES stent provides a broader stent expansion range (3.5–6.0 mm) to overcome the issue of size mismatch between proximal and distal vessel diameters. Improved axial and radial strength allows for the successful treatment of heavily calcified, fibrotic and ostial lesions.[6] Long-term complications with TLR are reduced by both the performance of post-PCI IVUS with large MSA compared to small MSA.[7] Our study demonstrates the ability of the Synergy Megatron platform to produce a mean LMS MSA that is numerically superior to that seen in the well-known EXCEL[27] and NOBLE[30] trials which studied LMS PCI cases (17 ± 3.9 mm^2 vs 12.5 ± 3.0 mm^2 vs 9.9 ± 2.3 mm^2, respectively).

A previous study of 139 patients undergoing PCI using the Synergy Megatron DES had demonstrated a low rate of 0.7% of patients having short-term MACE events with no cases of acute/subacute stent thrombosis.[31] Our study demonstrates similarly low rates of MACE events and no acute complications post-LMS PCI with the Megatron DES.

LIMITATIONS

This study has limitations, given the retrospective nature of data analysed. In addition, there was no control group for comparison with other stent technology. The short follow-up period and relatively small number of patients in this study limit conclusions that can be drawn and mean that it is underpowered to detect events such as stent thrombosis.

CONCLUSION

This study demonstrates low rates of short-term major adverse cardiovascular events among patients with LMS PCI using the Megatron stents. It highlights the usefulness of IVUS-guided optimisation in LMS PCI. With the use of intravascular imaging, the new generation stent technology can improve the treatment of large proximal vessels and PCI of LMS lesions.

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Sturge–Weber syndrome and variability of clinical presentation

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ABSTRACT

Introduction: Sturge–Weber syndrome (SWS) is a congenital syndrome characterised by intellectual disability, glaucoma, a characteristic port-wine stain on the skin around the route of the ophthalmic branch of the trigeminal nerve and the affection of the leptomeninges in the brain in the form of abnormal capillary venous vessels. The aim of this study is to look at the clinical features as well as the correlation of SWS with other comorbidities in hospitalised children.

Materials and methods: Records of admitted children over the period 2000–2019 were retrospectively studied. Epidemiological variables, gender and age at the time of diagnosis, changes in the skin, central nervous system affection and ophthalmological changes were analysed and recorded.

Results: Eleven cases of SWS were identified and included in the study. Age at the time of diagnosis ranged from 1 to 36 months. EEG showed specific grapho-elements, with partial seizures presenting in five cases out eight total cases with epilepsy. Ophthalmological complications were common, with glaucoma and choroidal haemangioma being the most common. Cognitive problems were found in seven cases, headache in eight cases and hemiparesis in four.

Conclusion: SWS is associated with other medical conditions. The study has described some of the features of SWS and found its correlation with epilepsy and other neurological problems, glaucoma, headache, hemiparesis and cognitive problems.

KEYWORDS:
Glaucoma, Port wine stain, Leptomeningeal angioma, epilepsy

INTRODUCTION

Sturge-Weber syndrome (SWS) is a congenital syndrome characterised by intellectual disability, glaucoma, a characteristic port-wine stain on the skin around the route of the ophthalmic branch of the trigeminal nerve and the affection of the leptomeninges in the brain in the form of abnormal capillary venous vessels.[1] It is caused by a somatic mutation in the gene GNAQ.[2] According to the National Organisation for Rare Disorders, SWS occurs in one of every estimated 20,000 to 50,000 live births.[3] The medical term for this disease is encephalotrigeminal angiomatosis but it can also be named as craniofacial angiomatosis.[3] Sturge–Weber can cause a number of complications, including seizures, developmental delays, muscle weakness on one side of the body, paralysis, cognitive impairment and eye problems.[3,4] In some children, however, the abnormal vessels characteristic for the disease can be asymptomatic.[6,7] Two out of every three children with SWS will have seizures. They may start at birth or in the first year of life. They are usually focal (also called partial) motor seizures involving jerks of one side of the body only. The seizures may become generalised and evolve into other types of seizures, such as atonic seizures 'drop attacks', myoclonic seizures or infantile spasms.[2,3] The abnormal blood vessels may also involve the eye directly and result in an abnormality of the drainage of fluid within the eye.[8,7]

According to the American Association for Paediatric Ophthalmology and Strabismus, an estimated 50% of children with SWS develop glaucoma during infancy or later in childhood. Glaucoma is an eye disease often caused by increased pressure in the eye. This can cause vision impairment, sensitivity to light and eye pain.[9,10]

Learning disabilities are present in two out of three children with SWS. In some children, severe learning disabilities develop. The more frequent and the more severe the seizures, the greater the severity of the learning disabilities.[11,12] The diagnosis of SWS is usually relatively easy. This is because of the characteristic 'port-wine' birth mark on one side of the face and neck is seen at or soon after birth. However, sometimes the diagnosis is more difficult. This is when the birth mark is very pale or occurs only over the scalp and is covered by the child's hair. A computerised tomography (CT) scan of the brain will usually show the typical abnormalities of the blood vessels on the surface of the brain better than a magnetic resonance imaging (MRI) brain scan.[7,11,13,14]

Treatment is mainly directed towards trying to control the frequent seizures and monotherapy does not produce good results. In these cases, early consideration should be given to epilepsy brain surgery. The surgery involves disconnecting part of the brain in the region of the abnormal blood vessels. This is called a 'hemispherotomy.'[6,2,15] Treatment of glaucoma, if it develops, is possible and laser treatment may be very effective for the birth marks.[8,16]

Through this study, we aimed to evaluate the clinical features of the disease in our country, its correlation with epilepsy and

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Table I: Structure of patients with SWS by sex and comorbidity

Sex	No.	%	*p* value
Female	5	45.5	0.76
Male	6	54.5	
Total	11	100.0	
Comorbidity			
Without comorbidity	3	27.3	0.13
With comorbidity (epilepsy)	8	72.7	
Total	11	100.0	

[a]Chi-square test was applied

Table II: Descriptive statistics for patients with SWS – age of diagnosis (n=11)

Age at diagnosis (day)		Statistic	Std. Error
Mean		540.27	124.43
95% Confidence Interval for Mean	Lower Bound	263.02	
	Upper Bound	817.52	
5% Trimmed Mean		539.41	
Median		365.00	
Std. Deviation		412.69	

Table III: Clinical characteristics of patients with SWS and neurological symptoms (n=8)

Type of seizures	No.	%	*p* value
Partial seizures	5	62.5	0.28
Mixed seizures	3	37.5	
EEG manifestations			
Specific electrical manifestations into one hemisphere	5	62.5	0.28
Specific electrical manifestations into two hemispheres	3	37.5	
Treatment			
Carbamazepine	2	25.0	0.61
Valproic acid+Levetiracetam	2	25.0	
Carbamazepine+Levetiracetam+Clonazepam	4	50.0	
Complications			
Ophthalmological	6	54.5	
Cognitive problems	7	63.6	
-lack of concentration, learning disorder	4	36.4	
-severe behavioral disorders	3	27.3	
Headaches	8	72.7	
-migraine headache	6	54.5	
-tension headaches	2	18.2	
Hemiparesis	4	36.4	
Changes in the face and nervous system	3	27.3	

[a]Chi-square test was applied.

Table IV: Treatment of patients with ophthalmological problems (n=6)

Ophthalmological treatment	No.	%	*p* value
Surgery (trabeculotomy-trabeculectomy)	4	66.7	0.41
Conservative treatment	2	33.3	
Total	6	100.0	

[a]Chi-square test was applied.

other neurological problems, glaucoma, headache, hemiparesis, and the impact of the disease on psychomotoric developmental delay.

MATERIALS AND METHODS

This is a retrospective cohort study and includes analysis of medical records of children admitted during the period of 2000–2019. Following this analysis, 11 cases with Sturge Weber syndrome have been identified, according to International Classification of Diseases (ICD-10). The study was undertaken at the University Clinical Centre of Kosovo, the referral and the only tertiary health care institution, covering cases referred from the entire country.

The data taken from the medical records include epidemiological variables, gender, age at the time of diagnosis, changes in the skin, changes in central nervous

system and ophthalmological changes. Other signs of central nervous system affection (development of epilepsy or not, hemiparesis, psychomotor disturbances, headache attacks), treatment of seizures, treatment of ophthalmological problems, imagery changes (central nervous system computerised tomography and magnetic resonance imaging) and electroencephalography changes, were analysed too.

In order to undertake and publish the study, informed consent and approval by Ethics and Professional Committee of Hospital and Clinical University Centre of Kosova were obtained, holding a decision number 3426, on November 11th, 2019.

The following statistical parameters have been used: the structure index, cumulative structure, simple arithmetic mean, standard deviation, standard error, confidence interval with a significance level of 95% (CI 95%). For the purpose of testing the differences for categorical data, chi-square test (chi-test), for the exact level of significance (p) has been used. The statistical tool used to analyse the date was Statistical Package for the Social Sciences (SPSS).

RESULTS

11 cases have been included in the study, six males and five females with a ratio of 55% to 45% (Table I).

When analysing the association of the disease with comorbidities, it has been identified that 8 cases (73%) have been associated with epilepsy. Age at the time of diagnosis ranged from 1 to 36 months, with a mean of 18 months (Table II).

Most of the seizures, 5 cases (63%), were partial while 3 cases (37%) were combined (atonic, partial with secondary generalisation, and generalised (Table III). EEG showed specific grapho-elements in one of the hemispheres in 4 cases (50%) (Table III). In 4 other cases (50%), specific grapho-elements are seen in both hemispheres. Specific grapho-elements include spike, spike-wave complex and low voltage in one of the hemispheres, slow wave activity and polyspike (Table III). With regard to the therapy, anticonvulsive drugs of different spectre have been used. Carbamazepine has been used successfully as monotherapy in 2 cases (25%), sodium valproate combined with levetiracetam resulting in partial seizure control in 2 cases (25%). Three antiepileptic drugs (carbamazepine, levetiracetam, clonazepam) have been used in 4 other cases (50%) with no full seizure control (Table III). Brain surgery such as hemispherectomy has not been undertaken in any of the cases. Hemiparesis was found in 4 cases (36%) and usually in contralateral side to facial and brain changes. Three cases (17%) presented with only facial changes and brain changes (Table III). Cognitive problems have been found in 7 cases (64 %). Cognitive problems were in direct correlation with the onset of seizures, the early the seizures started, more severe the cognitive problems. Also, cognitive problems were more severe in patients using two and more antiepileptic drugs. The commonest problems include attention deficit, learning disability in 4 cases (57%) and severe behavioural problems in 3 cases (43%) (Table III). Often, the level of behavioural problems depends on associated symptoms found in different patients, the more clinical manifestations, the greater the severity of behavioural problems. Headache of different nature has been found in 8 cases (73%), mostly migraine-type headache in 6 cases (75%) and tension type in 2 cases (25%) (Table III).
Ophthalmological complications are common. Six cases have associated glaucoma and choroidal haemangioma (55 %) (Table III).

In most of the patients, glaucoma was congenital and associated with choroidal haemangioma. Usually, ophthalmological changes were unilateral and ipsilateral to the facial changes. In order to prevent atrophy of optic nerve and increased intraocular pressure (IOP), combined surgical therapy was conducted in 4 cases (67%) and conservative therapy in 2 cases (33%). Trabecolotomy-trabeculectomy has been performed as a surgical method, and prostaglandins, beta blocker and anhydrase inhibitors (Table IV).

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DISCUSSION

Sturge-Weber syndrome is a rare disease, first mentioned by Schirmer (1860), and then described more by Sturge in 1879.[14] SWS has been classified in the group of rare diseases. According to the National Organisation for Rare Disorders, SWS occurs in one of every estimated 20,000 to 50,000 live births.3 There is no significant difference between male and female (6:5 in favour of male).[7] Glaucoma presents in 55% of the cases and is often associated with choroidal haemangioma, which also matches with data of many authors.[8,7,17] In most of the cases, a combination of surgical and conservative methods have been used to treat glaucoma.[15] About 73% of the patients have associated epilepsy, presenting with different type of seizures, in particular partial at the beginning of the disease evolving into secondary generalisation in older patients. The earlier the onset of seizures, the greater resistance to anticonvulsive therapy was noted.[5,11,17,2] Two and more anticonvulsive drugs have been used in most of the cases (75%) with no full seizure control. EEG revealed a range of changes, from focal to generalised, including different grapho-elements such as slow wave activity, spike wave complex, polyspike and low voltage. The same changes have been described by different authors.[5,11,17.2] Headache was present in 8 cases (73%), mostly migraine type.[6,13,14] Hemiparesis is seen in 4 cases (36%), involving contralateral side to changes in brain hemispheres.[11] A significant number of patients have psychomotoric developmental delay of different types (64%).[12] The level of psychomotoric delay depends on the time of seizure onset and number of abnormalities in other systems.

Sturge-Weber syndrome belongs to facomatosis group of diseases. The disease is associated with abnormalities in other systems, too. About 74% of cases are associated with epilepsy. EEG changes in most of the cases are partial. Treatment is complex because monotherapy does not produce good results. Carbamazepine is the most effective drug. The most common ophthalmological problem (55%) includes glaucoma and choroidal haemangioma. Glaucoma requires surgical and conservative intervention. Headache is quite common (73%), mostly migraine type. Cognitive problems are found in 64% of the cases, including speech disturbances, aggressive behaviour, and memory problems. Hemiparesis is not rare in children with SWS, it has been found in 34% of the cases. 17% of the cases presented with only facial and brain changes and no symptoms that could impact the quality of life. Diagnostic methods mostly used are computerised tomography, magnetic resonance imaging, doppler brain ultrasonography and fundoscopy.

The study has detected cases with rare SWS and its associated conditions as described in the literature, and described their complexity, especially in terms of inability to achieve the full seizure control, through monotherapy or combined drugs, in those presenting with seizures.

LIMITATION

In order to achieve a better seizure control, no hemispherectomy has been performed in any of the cases therefore a limitation is noted in terms of bringing our experience in this regard. Although the total number of cases was not high, most of the associated conditions were found in these cases, which gives an opportunity to further analyse each of them and extend the studies in the future to their specific management and outcomes.

CONCLUSION

To our best knowledge, this is the first study conducted in our country related to SWS in paediatric population. The results present the clinical characteristics of our patients, including the comorbidities and complications. As such, they are beneficial and useful for our further studying and planning.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Characteristics of electroencephalogram changes and correlation with seizures in hospitalised patients

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ABSTRACT

Introduction: Electroencephalogram (EEG) is an important investigational tool that is widely used in the hospital settings for numerous indications. The aim was to determine factors associated with abnormal EEG and its clinical correlations in hospitalised patients.

Materials and Methods: Patients with at least one EEG recording were recruited. The EEG and clinical data were collated.

Results: Two hundred and fifty patients underwent EEG and 154 (61.6%) were found to have abnormal EEG. The abnormal changes consist of theta activity (79,31.6%), delta activity (20, 8%), focal discharges (41,16.4%) and generalised discharges (14, 5.6%). Older patients had 3.481 higher risk for EEG abnormalities, *p*=0.001. Patients who had focal seizures had 2.240 higher risk of having EEG abnormalities, *p*<0.001. Low protein level was a risk for EEG abnormalities, *p*=0.003.

Conclusion: This study emphasised that an abnormal EEG remains a useful tool in determining the likelihood for seizures in a hospital setting. The risk factors for EEG abnormality in hospitalised patients were age, focal seizures and low protein level. The EEG may have an important role as part of the workup in hospitalised patients to aid the clinician to tailor their management in a holistic manner.

KEYWORDS:
Electroencephalogram, hospital

INTRODUCTION

Electroencephalogram (EEG)is a safe and non-invasive investigation to record electrical cerebral activity[1] and plays an important diagnostic and therapeutic role in neurological diseases. The advent of EEG by Hans Berger in 1929 began when he recorded cortical oscillatory activity from the surface of the skull in humans.[2] Scalp electrodes record the electrical brain activity which reflects the summation of excitatory and inhibitory postsynaptic potentials in apical dendrites of pyramidal neurons in the more superficial layers of the cortex.[3]

The association between cortical frequency bands of delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (12–28 Hz) and gamma (>30 Hz) oscillations with different behavioural and disease states have been explored.

EEG enables the assessment of neural activity of the cerebral cortex in normal and disease states. It is widely used in hospital settings for numerous conditions such as epilepsy, delirium, encephalopathy,[4] drug toxicity, status epilepticus and treatment monitoring. Microstates in resting state EEG for diagnosis of neurological disorders such as schizophrenia, dementia, and depression have been studied by Khanna et al.[5] The diagnostic validation of brain death in France requires two EEG recordings that showed electrocerebral inactivity.[6] Long-term EEG monitoring aids in the detection of epileptiform activity in high-risk seizure-free individuals.[7]

Hospitalised patients are prone to various co-morbidities such as infection, malnutrition, altered mentation, and drug effects. The detection of cerebral dysfunction of hospitalised patients can be easily demonstrated by performing the EEG. Continuous EEG monitoring had been found to be associated with reduced in-hospital mortality.[8] Detection of non-convulsive seizures and non-convulsive status epilepticus using continuous EEG are important in critically ill patients.[9] Seizures are invariably associated with clinical[10], metabolic[11] and electrophysiological changes.[12]

Well-defined EEG patterns have been associated with specific conditions and outcomes in encephalopathic patients.[4,13] Pathologic EEG patterns have been identified in hospitalised patients with encephalopathy. Frontal intermittent rhythmic delta activity and triphasic waves were associated with past cerebrovascular accidents and liver or multiorgan failure, respectively.[4]

Many investigations are performed in hospital to determine the diagnosis and management of the patients. The role of EEG in hospitalised patients is still underutilised. There is still a paucity of data on the variable factors that affect EEG changes in hospitalised patients. The aim of this study was to determine the patterns and associations of abnormal EEG patterns in hospitalised patients in a tertiary hospital.

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MATERIALS AND METHODS

This was a retrospective review carried out at the Neurology Laboratory, Universiti Kebangsaan Malaysia Medical Centre from October 2021to October 2022. The study was approved by the local Institution Research and Ethics Board (FF-2021-366). This study was carried out with written informed consent from all the subjects in accordance with the Declaration of Helsinki. We included hospitalised patients in the medical wards who had performed at least 1 EEG recording while patients with acute psychosis, nonepileptic seizures,critically ill patients, brain trauma and severe agitation were excluded. The patients were recruited by the purposive sampling method.

EEG was conducted in the awake state following application of surface electrodes according to the 10-20 system. Hyperventilation and photic stimulation activation procedures were carried out. The montages may be adjusted accordingly during the interpretation of the EEG. The EEG records were obtained using the filters of 1 Hz high-pass, 30 Hz low-pass and 60 Hz notch filters at a speed of 30 mm/s. Results from the routine scalp EEG recording were obtained through the EEG records reported by two neurologists and inter-rater agreement was determined. The report was classified as normal or abnormal. Normal EEG consists of 8–13 Hz alpha rhythm. Abnormal EEG findings include the following changes: 4–7 Hz theta activity, less than 3.5 Hz delta/slow activity, focal discharges or generalised discharges. The data of the patients were obtained from their records to determine the demographics, comorbidities, types of seizures, causes of seizures and investigations for seizures such as brain imaging such as computed tomogram or magnetic resonance imaging. The causes of seizures were classified into structural, infection, genetic, metabolic, immunologic and drugs. A structural cause refers to abnormalities visible on structural neuroimaging. A known infection cause refers to seizures which are a core symptom of the disorder. A genetic cause results directly from a known or presumed genetic disorder. A known or presumed metabolic disorder in which seizures are a core symptom of the disorder. An immune cause results directly from an immune disorder in which seizures are a core symptom of the disorder. A drug cause results directly from a known or presumed drug aetiology.

Statistical Analysis

Data were explored and analysed using SPSS software version 21.0. Numerical variables were presented using mean and standard deviation. The data were checked for normality. Categorical variables were presented as frequency and percentage. Distributions of continuous variables were compared using Student's t-tests; Pearson's chi-square tests or Fisher's exact tests were used for distributions of categorical variables. Statistical significance was defined by a p value of less than 0.05. Simple and multiple logistic regressions were used to determine the factors associated with electroencephalogram abnormalities. All odds ratios (ORs) are presented with 95% confidence intervals (CI).

RESULTS

Out of 250 patients, 131(52.4%) were male while females contributed 119 (47.6%). The highest group was contributed by patients in the age range between 61 and70 years(43,17.2%), followed by 31 to 40 years (39, 16.6%) and 71 to 80 years (38, 15.2%). The Malay ethnicity accounted for 122 (48.8%), followed by Chinese 93 (37.2%), Indian 29 (11.6%), and others 6 (2.4%). %). The main diagnoses for the patients were post-stroke seizures, meningoencephalitis, epilepsy with breakthrough seizures and sepsis. As for the distribution of electroencephalogram abnormalities, 154 (61.6%) were found to be abnormal readings while 96 (38.4%) had normal EEG. The distribution of EEG changes consists of normal (96,38.4%), theta activity (79,31.6%), delta activity (20, 8%), focal discharges (41,16.4%) and generalised discharges (14, 5.6%). The brain imaging findings consisted of cerebral atrophy, tumour, abscess, stroke, encephalomalacia, neurofibroma, meningeal enhancement and normal.

Table I shows the demographics of patients with and without EEG abnormalities. There was significant association between age, race, seizure type and brain imaging with EEG abnormalities.

Table II shows clinical parameters in patients with and without EEG abnormalities. There was no significant association between causes of seizure, laboratory parameters and EEG abnormalities. However, only protein level was significantly associated with EEG abnormalities (p<0.001).

The distribution of patient characteristics according to seizure types was as follows: no seizures (147, 58.8%), generalised seizures (73, 29.2%) and focal seizures (30, 12%). The proportion in the young age group (15–64) years were no seizures (83, 49.4%), generalised seizures (61,36.3%) and focal seizures (24, 14.3%). In comparison, the old age group (65–95) years were no seizures (64, 78%), generalised seizures (12, 14.6%) and focal seizures (6, 7.3%). Only age had significant association with seizure types (p<0.001). Both gender and race did not show any significant difference. The proportion of male to female in the group with no seizures were (81, 55.1%; 66, 44.9%), generalised seizures (37, 50.7%; 36, 49.3%), and focal seizures (13, 43.3%; 17, 56.7%). The proportion of Malay to non-Malay in the group with no seizures was(78, 53.1%; 69, 46.9%), generalised seizures (37, 50.7%; 36, 49.3%) and focal seizures (13, 43.3%; 17, 56.7%).

Table III shows the risk factors associated with EEG abnormalities. In simple logistic regression, the risk factors associated with EEG abnormalities were age, race, hypertension, brain imaging, focal seizures and protein level (p<0.005). Multiple logistic regression demonstrated that older patients had 3.481 higher risk than younger patients of having EEG abnormalities (adjusted OR=3.481; 95% CI 1.615, 7.500, p=0.001). Patients who had focal seizures had almost 2.240 higher risk of having EEG abnormalities (adjusted OR=2.240; 95% CI 1.425, 3.521, p<0.001). Low protein level has a significant risk with EEG abnormalities (adjusted OR=0.409; 95% CI 0.229, 0.731, p=0.003).

Table I: Demographics of patients with and without EEG abnormalities

	Without EEG abnormalities N=96		With EEG abnormalities N=154		*p* value
	Mean (SD)	n (%)	Mean (SD)	n (%)	
Sociodemographics					
Age (years)	46.31 (17.67)	96 (38.40)	56.47 (20.80)	154 (61.60)	<0.001 [a]
Young (15-64)		80 (83.3)		88 (57.1)	
Old (65-95)		16 (16.7)		66 (42.9)	
Gender					
Male		54 (56.20)		77 (50.0)	0.336 [b]
Female		42 (43.80)		77 (50.0)	
Race					
Malay		56 (58.3)		66 (42.9)	0.034 [b]
Chinese		32 (33.3)		61 (39.6)	
Indian		8 (8.3)		21 (13.6)	
Others		0 (0)		6 (3.9)	
Seizure type					
None		61 (63.5)		86 (55.8)	0.033 [b]
Generalized		30 (31.3)		43 (27.9)	
Focal		5 (5.2)		25 (16.2)	
Brain imaging					
Normal		37 (48.1)		40(51.9)	0.037 [b]
Abnormal		58 (34.1)		112 (65.9)	

[a]Student's t test
[b]Pearson's Chi-Square test

Table II: Clinical parameters in patients with and without electroencephalogram abnormalities

	Without EEG abnormalities N=96		With EEG Abnormalities N=154		*p* value
	Mean (SD)	n (%)	Mean (SD)	n (%)	
Causes of seizure					
Structural	46.31 (17.67)	96 (38.40)	56.47 (20.80)	154 (61.60)	<0.001 [a]
No		74 (39.6)		113 (60.4)	0.511 [a]
Yes		22 (34.9)		41 (65.1)	
Infection					
No		34 (31.2)		75 (68.8)	0.23 [a]
Yes		6 (20.0)		24 (80)	
Genetic					
No		36 (29.3)		87 (70.7)	1 [b]
Yes		4(25.0)		12 (75)	
Metabolic					
No		40 (29.9)		94 (70.1)	0.321 [b]
Yes		0 (0.00)		5 (100)	
Immunologic					
No		96(39.0)		150(61)	0.301 [b]
Yes		0 (0.00)		4 (100)	
Drugs					
No		96 (38.9)		151(61.1)	0.288 [b]
Yes		0 (0.00)		3(100)	
Laboratory parameters					
Haemoglobin	12.93 (2.67)		12.81 (8.38)		0.455 [c]
White cell count	11.43 (13.62)		11.53 (7.59)		0.779 [c]
Platelet	277.79 (107.86)		271.23 (123.26)		0.225 [c]
Urea	5.29 (4.40)		11.59 (47.78)		0.101 [c]
Creatinine	126.55 (202.69)		125.02 (146.98)		0.647 [c]
Protein	73.11 (8.41)		68.05 (10.84)		<0.001 [c]
Alanine transaminase	31.31 (28.49)		34.79 (33.15)		0.248 [c]

[a] Pearson's Chi Square Test
[b] Fisher's Exact Test
[c] Student's test

Table III: Risk factors associated with electroencephalogram abnormalities

Variables	Simple logistic regression			Multiple logistic regression		
	b	Crude OR (95% CI)	p	b	Adjustment OR (95% CI)	p
Age	1.322	3.750 (2.08–7.002)	<0.001	1.247	3.481(1.615–7.500)	0.001
Race	-0.624	0.536(0.320–0.898)	0.018	–0.244	0.784 (0.439–1.399)	0.410
Hypertension	-0.705	0.494(0.293–0.835)	0.008	0.339	1.404 (0.729–2.703)	0.310
Brain imaging	0.580	1.786(1.033–3.090)	0.038	0.000	1.000(0.973–1.029)	0.983
Focal seizures	1.266	3.547(1.286–9.783)	0.014	0.806	2.240 (1.425–3.521)	<0.001
Protein level	–1.836	0.159(0.055–0.466)	0.001	–0.893	0.409(0.229–0.731)	0.003

OR, odds ratio; b, regression coefficient; CI, confidence interval

Table IV: Distribution of patients according to seizure occurrence

	No seizures	Seizure	*p* value
	N=142	N=105	
	n (%)	n (%)	
Age (years)			
Young (15–64)	81 (57.0)	86 (81.9)	<0.001 [a]
Old (65–95)	61(43.0)	19 (18.1)	
Gender			
Male	79(54.5)	52(49.5)	0.438 [a]
Female	66(45.5)	53(50.5)	
Race			
Malay	76 (53.5)	51(48.6)	0.442 [a]
Non-Malay	66(46.5)	54(51.4))	
Hypertension			
No	59(41.5)	75(71.4)	<0.001 [a]
Yes	83 (58.5)	30 (28.6)	
Diabetes mellitus			
No	84(59.2)	89 (84.8)	<0.001 [a]
Yes	58(40.8)	16 (15.2)	

[a]Student's t test.

Table V: Risk factors associated with seizures occurrence

Variables	Simple logistic regression			Multiple logistic regression		
	b	Crude OR (95% CI)	*p*	b	Adjustment OR (95% CI)	*p*
Age	–1.226	0.293 (0.161–0.533)	<0.001	–0.775	0.461(0.190–0.750)	0.027
Hypertension	1.258	3.517 (2.051–6.030)	<0.001	–0.587	0.556(0.289–1.068)	0.078
Diabetes mellitus	1.346	3.841 (2.048–7.202)	<0.001	–0.973	0.378 (0.190–0.750)	0.005

OR, odds ratio; b regression coefficient; CI, confidence interval.

Table IV shows the distribution of patient characteristics according to seizure occurrence. Age, hypertension and diabetes mellitus have a significant association with developing seizures.

Table V presents the risk factors associated with seizure occurrence. Multiple logistic regression showed that risk factors included age and diabetes mellitus.

DISCUSSION

This study focussed on hospitalised patients in a tertiary hospital in Malaysia. We reported a prevalence of 61.6% EEG abnormalities in our cohort of patients. Another study from a tertiary centre from Karachi[14] obtained EEG records from consecutive patients from the neurology department quoted almost similar results with 60.2% of patients with abnormal EEG records. Another hospital-based setting studyfound abnormal EEG patterns in patients with altered mental status who were subdivided into structural causes (brain atrophy, white matter abnormalities, strokes) and non-structural causes (organ failures, intoxication, infections).[4] However, previous studies only conducted EEG on a selected group of patients such as intensive care patients,[15] epilepsy,[16] psychiatric[17] and encephalopathic[18] patients.

The type of EEG abnormalities found in this study was comparable to other studies. The proportion of theta activity (31.6%), delta activity (8%), focal discharges (16.4%) and generalised discharges (5.6%). Apart from theta and delta activity, Sutter et al[4] reported findings of triphasic waves 22% and frontal intermittent rhythmic delta activity (FIRDA) 17%. Younger patients were also more likely to have FIRDA and delta activity. The EEG changes obtained from a cohort of inpatients from a tertiary centre found diffuse neuronal dysfunction in 45.2% and mild neuronal dysfunction accounted for 33.5%.[14] A Nigerian based study had found 56% of patients with epileptiform activity[17] in a psychiatric-based hospital. A case–control study of EEG microstate analysis found a decreased in the microstate stability in the inpatient encephalopathy group.[19] Our study reported higher proportion of abnormal EEG as it included a heterogenous

pool of hospitalised patients who were admitted for various medical conditions.

The type of EEG abnormality has been shown to be associated with risk of seizures. In a multicentre cohort study of critically ill adult patients, EEG monitoring that showed lateralised periodic discharges, lateralised rhythmic delta activity, and generalised periodic discharges were associated with seizures.[18] On the contrary, generalised rhythmic delta activity had no association with seizures. Our study determined that focal seizures are invariably linked to the presence of EEG abnormalities. Focal-onset seizures originate from one hemisphere and may be discretely localised to a particular site. The patients who had focal seizures were found to have almost 2.240 higher risk of having EEG abnormalities. Similarly, another study by Manford et al found 75.9% had EEG abnormalities in focal seizures.[10]

Our findings emphasised that focal seizures had higher risk to develop EEG abnormalities. Temporal lobe epilepsy is the most common focal epilepsy, and therefore, interictal temporal spikes or sharp waves are commonly observed. Focal seizures are likely to have interictal epileptic discharges and lateralised ictal EEG changes.[20] The use of ictal EEG adequately localises in 72% of cases, largely in temporal epilepsy rather than extratemporal epilepsy. Localised ictal onsets were observed in 57% of seizures.[20] The presence of focal spikes and focal slow waves on EEG also predicts the likelihood of developing uncontrolled seizures.[21]

From our study, the age-related EEG abnormalities were more significant in older patients compared to younger patients. There is a progressive change in brain wave frequency, power, morphology and distribution during rest with ageing.[22] In a study of pathological brain on EEG changes, elderly people showed decrease in alpha oscillatory activity and alpha rhythm reactivity as well as slowing of the background activity, with an increase in delta or theta power diffusely or in posterior region rhythm abnormalities, which are linked to poor cognitive performance.[22] Jabes et al reported the resting-state brain activity of healthy older adults (65–75 years old) exhibited lower theta-band and alpha-band and absolute powers, and higher beta-band and gamma band relative powers were observed compared to healthy young adults (20–30 years old).[23] A study of ageing-related changes of EEG synchronisation revealed differences in old and young adults during working memory task.[24] It was observed that older adults had lower EEG synchronisation in alpha 1, alpha 2 and beta frequency bands which reflects the decline in cognitive function.[24] The study's findings concurred with previous epidemiological studies that showed that elderly population has a high incidence and prevalence of epilepsy.[25] The elderly population are prone to seizures due to the various comorbidity that includes stroke, brain tumours, infections, head trauma, dementia and metabolic-toxic syndromes. The utilisation of EEG to determine changes in the neuropsychological aspects has improved the understanding of diseases in the elderly.

The effects of nutrition on cognitive function have been well recognised. Our study has revealed that protein level was a risk factor for EEG abnormalities in hospitalised patients. Those who have a low protein level would have a greater chance of having an abnormal EEG finding. In a study of seizures and malnutrition, Stern et al[26] revealed that protein malnutrition could lead to enhanced seizure susceptibility. Protein energy malnutrition exhibited EEG abnormalities in childhood such asdevelopmental delay in alpha rhythm maturation and an insufficient decrease in beta activity.[27] In a study ofchildren with malnutrition, EEG abnormalities demonstrated the presence of slow and sharp waves in the frontal, parietal and temporal lobes.[28] Quantitative EEG analysis in protein energy malnutrition in children demonstrated an increase in theta activity, decrease in alpha 1 in fronto-central electrodes, increase in fast alpha in temporo-parietal electrodes and increase in beta activity in temporal leads.[29] However, most of these studies focussedon children and further studies are required to elucidate the effect of malnutrition on EEG changes in the adult population.

LIMITATIONS

This was a single-centre study being carried out, so the data may not be representative of the general population. As there were multiple comorbidities from the cohort, the subanalysis of each medical condition with the EEG abnormalities did not reach any statistical significance. Thus, a larger sample size may be required to study the effect of medical conditions on EEG abnormalities. Another limitation is that this work detailed only a single initial EEG in the patients. A repeated EEG may be useful to detect any evolving changes from the baseline EEG. As the EEG was analysed retrospectively, any abnormalities such as the presence of seizure activity may warrant urgent medical attention. However, the EEG records were reviewed by the neurologists who had commenced the appropriate treatment.

CONCLUSION

This study emphasised that an abnormal EEG remains a useful tool in determining the likelihood of seizures in a hospital setting. The risk factors for EEG abnormality in hospitalised patients were age, focal seizures and low protein level. The EEG does have an important role as part of the workup in hospitalised patients to aid the clinician tailor their management in a holistic manner.

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CONFLICT OF INTEREST

We certify that there is no actual or potential conflict of interest in relation to this article.

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Clinical characteristics and computed tomographical features of pulmonary thromboembolic disease associated with COVID-19 infection: A tertiary hospital analysis

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ABSTRACT

Introduction: The co-existence of coronavirus disease 2019 (COVID-19) and pulmonary thromboembolic (PTE) disease poses a great clinical challenge. To date, few researches have addressed this important clinical issue among the South-East Asian populations. The objectives of this study were as follow: (1) to describe the clinical characteristics and computed tomographical (CT) features of patients with PTE disease associated with COVID-19 infection and (2) to compare these parameters with those COVID-19 patients without PTE disease.

Materials and Methods: This cross-sectional study with retrospective record review was conducted in Hospital Tengku Ampuan Rahimah, Selangor, Malaysia. We included all hospitalised patients with confirmed COVID-19 infection who had undergone CT pulmonary angiogram (CTPA) examinations for suspected PTE disease between April 2021 and May 2021. Clinical data and laboratory data were extracted by trained data collectors, whilst CT images retrieved were analysed by a senior radiologist. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.

Results: We studied 184 COVID-19 patients who were suspected to have PTE disease. CTPA examinations revealed a total of 150 patients (81.5%) suffered from concomitant PTE disease. Among the PTE cohort, the commonest comorbidities were diabetes mellitus (n=78, 52.0%), hypertension (n=66, 44.0%) and dyslipidaemia (n=25, 16.7%). They were generally more ill than the non-PTE cohort as they reported a significantly higher COVID-19 disease category during CTPA examination with *p*=0.042. Expectedly, their length of both intensive care unit stays (median number of days 8 vs. 3; *p*=0.021) and hospital stays (median number of days 14.5 vs. 12; *p*=0.006) were significantly longer. Intriguingly, almost all the subjects had received either therapeutic anticoagulation or thromboprophylactic therapy prior to CTPA examination (n=173, 94.0%). Besides, laboratory data analysis identified a significantly higher peak C-reactive protein (median 124.1 vs. 82.1; *p*=0.027) and ferritin levels (median 1469 vs. 1229; *p*=0.024) among them. Evaluation of CT features showed that COVID-19 pneumonia pattern (*p*<0.001) and pulmonary angiopathy (*p*<0.001) were significantly more profound among the PTE cohort. To note, the most proximal pulmonary thrombosis was located in the segmental (n=3, 2.0%) and subsegmental pulmonary arteries (n=147, 98.0%). Also, the thrombosis predominantly occurred in bilateral lungs with multilobar involvement (n=95, 63.3%).

Conclusion: Overall, PTE disease remains prevalent among COVID-19 patients despite timely administration of thromboprophylactic therapy. The presence of hyperinflammatory activities, unique thrombotic locations as well as concurrent pulmonary parenchyma and vasculature aberrations in our PTE cohort implicate immunothrombosis as the principal mechanism of this novel phenomenon. We strongly recommend future researchers to elucidate this important clinical disease among our post-COVID vaccination populations.

KEYWORDS:
COVID-19, pulmonary thromboembolic disease, clinical characteristics, computed tomographical features

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel virus has the potential to cause a multitude of deleterious effects on the host, ranging from acute respiratory distress syndrome, arrhythmia, acute myocardial injury, acute kidney injury and multi-organ failure.[1,2] Lately, the association of pulmonary thromboembolic (PTE) disease and COVID-19 infection has been increasingly recognised. The putative cause of this phenomenon is believed to be due to the combination of both prothrombotic state and widespread pulmonary microvasculature injury created by COVID-19-induced immune hyperactivation. Importantly, the co-existence of PTE disease with COVID-19 infection portends a poor prognosis.[3]

Computed tomography pulmonary angiogram (CTPA) remains to be the imaging modality of choice in the work-up

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of patients with suspected PTE disease. It has the ability to demonstrate thrombus as well as to delineate the thrombotic lesion location.[4] In addition, it also provides additional information which enables the clinician to distinguish between COVID-19 pneumonia changes from non-COVID related changes. To note, we experienced an unprecedented demand in CTPA examination during the peak of COVID-19 pandemic from late April until September 2021, whereby virtually all of our CT suites were running in full tilt during that crisis.

To our best knowledge, PTE disease associated with COVID-19 infection has not been well studied in South-East Asia and most of the data in the literature were generated from the Western populations.[5-7] In an effort to fill this knowledge gap, we undertook this study which aimed to describe the clinical characteristics and computed tomographical (CT) features of patients with PTE disease associated with COVID-19 infection, and compare these to the parameters with those COVID-19 patients without PTE disease.

MATERIALS AND METHODS

Study Setting

This study was conducted in Hospital Tengku Ampuan Rahimah (HTAR) which is a tertiary hospital located in the royal Klang district, Selangor, Malaysia. During the study period, HTAR was designated as a hybrid hospital that served to provide both in-patient treatment for COVID-19 as well as non-COVID 19 patients. In retrospect, Klang district was one of the worst-hit districts at that time. The provision of COVID-19 care was led by infectious disease specialists in close collaboration with multiple disciplines, which included intensivist, acute internal medicine physician, emergency physician, general physician, haematologist, respiratory physician, radiologist and microbiologist.

Study Design and Data Collection

This is a retrospective study that involves review of clinical notes as well as CTPA imaging of all hospitalised COVID-19 patients with suspected acute PTE disease between 1st April 2021 and 31st May 2021. The COVID-19 diagnosis was confirmed by either COVID-19 real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), GeneXpert or rapid antigen test (RTK) from nasopharyngeal swab or lower respiratory samples.

Additionally, only subjects who had undergone CTPA examination as well as aged ≥ 18-year-old would be included. In total, we excluded 13 subjects due to the following reasons: at-own-risk discharge (3 cases), severe CTPA image artefacts (1 case), onset of COVID-19 infection more than 30 days at presentation (2 cases), hospital-acquired COVID-19 infection (2 cases) and incomplete or clinical notes (5 cases). All data collected was entered into the pre-tested Google Form which served as the electronic case report form (eCRF) by the trained investigators.

Clinical and Laboratory Data

The clinical stages of COVID-19 were categorised as below: category 1 asymptomatic; category 2 symptomatic but no pneumonia; category 3 symptomatic with pneumonia; category 4a requiring nasal prong or face mask or venturi mask <60%; category 4b requiring high flow mask or venturi mask ≥60%; category 5a requiring non-invasive ventilation including high flow nasal cannula and category 5b mechanical ventilation with or without other organ failures.[8]

On another note, the day of COVID-19 illness was determined with reference to the clinical symptom onset date. In circumstances where the clinical history was unclear or the patient was asymptomatic during diagnosis, the first day of illness was calculated from the day the COVID-19 test first became positive.

Anticoagulant treatment received prior to or during CTPA examination was classified into three regimens, namely prophylactic anticoagulation, intermediate anticoagulation, and therapeutic anticoagulation. The definition of anticoagulation regimens was developed with reference to our institution protocol. Prophylactic anticoagulation is defined as (a) sc. enoxaparin 40mg–60mg daily (if eGFR ≥30 ml/min/1.73m^2); (b) sc. enoxaparin 20mg OD (if eGFR <30 ml/min/1.73m^2)and (c) sc. unfractionated heparin 5000 units q12 hourly or q8 hourly. Therapeutic anticoagulation is defined as (a) sc. enoxaparin 1mg/kg/BD (if eGFR ≥30 ml/min/1.73m^2); (b) sc. enoxaparin 1mg/kg/OD (if eGFR <30 ml/min/1.73m^2); (c) warfarin with INR ranged 2-3 and (d) direct oral anticoagulation therapy as per drug insert recommendation. Any dose in between prophylactic and therapeutic range would be considered as intermediate anticoagulation. In the situation where body weight was unavailable, the clinician would exercise his discretion to determine the anticoagulation regimen based on the clinical notes review.

Pertaining to the laboratory data, D-dimer level was reported in Fibrinogen Equivalent Units (FEU, µg/ml) and a value of less than 0.5 µg/ml was considered as negative. Also, any level above 20 µg/ml would be reported as >20 µg/ml.

The primary outcome measure was death during the hospital stay and 60-day mortality rate after being infected with COVID-19 infection. We did not attempt to determine whether the 60-day mortality was attributable to the PTE disease associated with COVID-19 in view of the retrospective nature of the study. Out-of-hospital death was verified with National Registration Department, Malaysia if such information was not available in our hospital.

Radiological Data

CT image acquisition

Computed tomography pulmonary artery (CTPA) examination was performed on 64-slice multi-detector CT scanners (Toshiba Aquillion CX). The whole chest was craniocaudally scanned from lung apices to the lowest hemidiaphragm for each patient in the supine position. All patients except for intubated cases were instructed to hold their breath to minimise motion artefacts, and CTPA images were acquired during a single breath-hold. Scan parameters were as follows: tube voltage of 120 kV, tube current of 100 to 300 mAs, collimation of 0.6 to 0.625 mm, table speed of 39.37 mm/s, and gantry rotation time of 0.5 s. The soft tissue reconstruction kernel was used. A volume of 50 to 60 mL

Table I: Socio-demographic and clinical characteristics of COVID-19 patients with suspected PTE

Characteristics	n (%)			*p* value
	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	
Age in years, mean (SD)	56 (13.2)	57 (12.6)	49 (14.1)	**0.002**[a]
Male gender	112 (60.9)	91 (60.7)	21 (61.8)	0.906[b]
With at least one comorbidity	134 (72.8)	110 (73.3)	24 (70.6)	0.745[b]
Comorbidities				
Diabetes mellitus	95 (51.6)	78 (52.0)	17 (50.0)	0.764[b]
Hypertension	80 (43.5)	66 (44.0)	14 (41.1)	0.833[b]
Dyslipidaemia	28 (15.2)	25 (16.7)	3 (8.8)	0.250[b]
Ischemic heart disease	19 (10.3)	17 (11.3)	2 (5.9)	0.534[c]
Obesity	5 (2.7)	4 (2.7)	1 (2.9)	1.000[c]
End stage renal disease	5 (2.7)	4 (2.7)	1 (2.9)	1.000[c]
Chronic kidney disease excluding ESRF	3 (1.6)	3 (2.0)	0 (0.0)	1.000[c]
Malignancy	1 (0.5)	1 (0.7)	0 (0.0)	1.000[c]
Other comorbid*	34 (18.5)	29 (19.3)	5 (14.7)	0.530[b]
Symptomatic at presentation	183 (99.5)	149 (99.3)	34 (100.0)	1.000[c]
Symptoms at presentation				
Cough	143 (77.7)	115 (76.7)	28 (82.4)	0.472[b]
Fever	129 (70.1)	106 (70.7)	23 (67.6)	0.728[b]
Shortness of breath	124 (67.4)	100 (66.7)	24 (70.6)	0.660[b]
Diarrhoea	57 (31.0)	49 (32.7)	8 (23.5)	0.298[b]
Fatigue	37 (20.1)	31 (20.7)	6 (17.6)	0.692[b]
Sore Throat	23 (12.5)	18 (12.0)	5 (14.7)	0.774c
Vomiting	20 (10.9)	16 (10.7)	4 (11.8)	0.768[c]
Anosmia	8 (4.3)	6 (4.0)	2 (5.9)	0.642[c]
Ageusia	8 (4.3)	7 (4.7)	1 (2.9)	1.000[c]
Other symptom#	101 (54.9)	84 (56.0)	17 (50.0)	0.526[b]
Temperature at presentation (degree Celsius), median (IQR)	37.9 (37.0- 38.7)	38.0 (37.0-38.8)	37.5 (36.9-38.2)	0.123[d]
Day of Illness at Presentation, median (IQR)	5 (4.0-7.0)	5 (3.0-7.0)	5 (4.0-7.0)	0.365[d]
Day of Illness during CTPA, median (IQR)	10 (8.0-13.0)	10 (8.0-13.0)	10 (8.0-13.0)	0.772[d]
Category of Illness during CTPA				**0.042**[c]
2	3 (1.6)	1 (0.7)	2 (5.9)	
3	4 (2.2)	2 (1.3)	2 (5.9)	
4a	70 (38.0)	56 (37.3)	14 (41.1)	
4b	44 (23.9)	34 (22.7)	10 (29.4)	
5a	34 (18.5)	30 (20.0)	4 (11.8)	
5b	29 (15.8)	27 (18.0)	2 (5.9)	
Treatment received during/prior to CTPA				
Inotropic support	24 (13.0)	23 (15.3)	1 (2.9)	0.086[c]
Systemic steroids	180 (97.8)	148 (98.7)	32 (94.1)	0.156[c]
Immunomodulators	65 (35.3)	58 (38.7)	7 (20.6)	**0.046**[b]
Favipiravir	129 (70.1)	111 (74.0)	18 (52.9)	**0.015**[b]
Anticoagulation regimen received within the last 48 hours prior to CTPA				0.092[c]
(a) Prophylactic low molecular weight heparin	134 (72.8)	108 (72.0)	26 (76.5)	
(b) Prophylactic unfractionated heparin	3 (1.6)	3 (2.0)	0 (0.0)	
(c) Therapeutic anticoagulation	34 (18.5)	31 (20.7)	3 (8.8)	
(d) Intermediate anticoagulation	2 (1.1)	2 (1.3)	0 (0.0)	
(e) None	11 (6.0)	6 (4.0)	5 (14.7)	
Inotropic support during admission	36 (19.6)	34 (22.7)	2 (5.9)	**0.026**[b]
Highest oxygen support during admission				**0.016**[c]
No oxygen required	7 (3.8)	3 (2.0)	4 (11.8)	**0.023**[c]
Nasal Prong	38 (20.7)	29 (19.3)	9 (26.5)	0.353[b]
Face Mask	21 (11.4)	19 (12.7)	2 (5.9)	0.375[c]
Venturi Mask 40%	1 (0.5)	0 (0.0)	1 (2.9)	0.185[c]
Venturi Mask 60%	11 (6.0)	9 (6.0)	2 (5.9)	1.000[c]
High Flow Mask	25 (13.6)	19 (12.7)	6 (17.6)	0.417[c]
High Flow Nasal Cannula	37 (20.1)	30 (20.0)	7 (20.6)	0.938[b]
Mechanical Ventilatory Support (Intubated)	44 (23.9)	41 (27.3)	3 (8.8)	**0.022**[b]
ICU admission	84 (45.7)	72 (48.0)	12 (35.3)	0.179[b]
Length of ICU stay, median (IQR)	8 (4.0-13.0)	8 (4.0-13.0)	3 (2.3-11.0)	**0.021**[d]
Length of hospital stay, median (IQR)	14 (10.0-19.0)	14.5 (11.0-20.0)	12 (10.0-14.0)	**0.006**[d]
Outcome				0.083[c]
Discharged	162 (88.0)	129 (86.0)	33 (97.1)	
In-hospital death	22 (12.0)	21 (14.0)	1 (2.9)	
Sixty-day all-cause Mortality	23 (12.5)	22 (14.7)	1 (2.9)	0.083[c]

SD, standard deviation; IQR, interquartile range

[a]Independent T-test [b]Pearson Chi-square [c]Fisher's Exact Test [d]Mann–Whitney U Test

*Other comorbid: Chronic obstructive pulmonary disease (COPD), bronchial asthma, bronchitis, congestive cardiac failure, old cardiovascular accident, Alzheimer's disease, dementia, Parkinson disease, bipolar disorder, anaemia, hereditary spherocytosis, fatty liver, benign prostate hypertrophy, gouty arthritis, obstructive sleep apnoea, hyperthyroidism, scleroderma, uterine fibroid, haemorrhoid, gastritis, slipped disc, rheumatoid arthritis

#Other symptom: runny nose, epistaxis, chills and rigours, pleuritic chest pain, haemotypsis, arthralgia, myalgia, loss of appetite, loss of weight, nausea, acid brash sensation, epigastric pain, diaphoresis, reduced urine output, orthopnea, paroxysmal nocturnal dyspnoea, dizziness, heaviness over head, pre-syncopal attack, syncope, hypoxia, reduced consciousness, unconscious, left sided body weakness, alleged fall and slurred speech

Table II: Laboratory data of COVID-19 patients with suspected PTE

Laboratory data	Normal range	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	*p* value
Full blood count parameter at presentation, median (IQR)					
Hb (g/dL)	12.0-15.0	13.4 (12.3-14.7)	13.4 (12.6-14.7)	13.7 (12.4-14.5)	0.788[a]
WCC (×10^9/L)	4.0-10.0	6.7 (5.1-8.7)	6.9 (5.2-8.9)	6.0 (4.8-8.1)	0.212[a]
ALC (×10^9/L)	1.0-3.0	1.0 (0.7-1.4)	1.0 (0.8-1.4)	1.1 (0.8-1.7)	0.335[a]
Platelet (×10^9/L)	150-410	220 (165.0-272.5)	208 (165.0-267.3)	240 (181.3-322.0)	0.088[a]
Peak level throughout admission, median (IQR)					
CRP (ng/L)	<5.0	119.4 (75.4-155.0)	124.1 (86.2-155.1)	82.1 (58.7-153.9)	**0.027**[a]
Ferritin (ug/L)*	10-291	1369 (648.0-2125.0)	1469 (688.0-2189.0)	1229 (197.5-1506.0)	**0.024**[a]
AST (U/L)	<34	73 (48.3-119.3)	73 (50.0-121.0)	59.5 (34.8-105.0)	0.077[a]
ALT (U/L)	10-49	90 (50.8-152.0)	92 (50.8-155.8)	78 (44.8-137.3)	0.202[a]
Creatinine (µmol/L)	44.2-97.2	97.1 (81.0-135.1)	97 (78.6-135.1)	94.3 (75.1-128.2)	0.366[a]
Procalcitonin (ng/ml)#	<0.05				0.171[b]
<0.05		22 (14.2)	14 (11.1)	8 (27.6)	
0.05–0.49		97 (62.6)	82 (65.1)	15 (51.7)	
0.50–2.00		23 (14.8)	19 (15.1)	4 (13.8)	
>2.00		13 (8.4)	11 (8.7)	2 (6.9)	
Peak level of D-dimer (µg/ml) pre-CTPA, n (%)	0-<0.5				0.242[b]
<0.5		10 (5.4)	7 (4.7)	3 (8.8)	
0.5–5.0		152 (82.6)	123 (82.0)	29 (85.3)	
5.1–20.0		12 (6.6)	12 (8.0)	0 (0.0)	
>20.0		10 (5.4)	8 (5.3)	2 (5.9)	

[a]Mann–Whitney U test.
[b]Fisher's Exact Test.
*Ferritin level was taken for 168 subjects (not taken for 16 subjects).
#Procalcitonin level was taken for 155 subjects (not taken for 29 subjects).

Table III: Radiological features of COVID-19 patients with suspected PTE

Radiological features	n (%)			*p* value
	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	
Covid-19 pneumonia/organising pneumonia changes				**<0.001**[a]
None	1 (0.5)	0 (0.0)	1 (2.9)	
Mild	62 (33.7)	48 (32.0)	14 (41.2)	
Minimal	16 (8.7)	6 (4.0)	10 (29.4)	
Moderate	63 (34.3)	56 (37.3)	7 (20.6)	
Severe	42 (22.8)	40 (26.7)	2 (5.9)	
Pulmonary angiopathy changes	51 (27.7)	50 (33.3)	1 (2.9)	**<0.001**[b]
Other computerized tomography (CT) findings*	81 (44.0)	76 (50.7)	5 (14.7)	**<0.001**[b]
Most proximal anatomical location	Not applicable		Not applicable	-
Segmental		3 (2.0)		
Subsegmental		147 (98.0)		
Degree of involvement	Not applicable		Not applicable	-
Single lobar, Unilateral		53 (35.4)		
Multilobar, Unilateral		2 (1.3)		
Multilobar, Bilateral		95 (63.3)		

[a]Fisher's Exact Test.
[b]Pearson Chi-square test.
*Other CT findings: Cardiomegaly, pneumomediastinum, pleural effusion, bronchiectasis with cavitation, aortic aneurysm, emphysema, pulmonary artery hypertension, lung fibrosis, interstitial lung disease, cholelithiasis, sclerotic bone lesion, liver cyst and breast lesion.

(calculated based on the patient's body weight) of non-ionic iodinated contrast medium (Ultravist 370) was injected into an antecubital vein at a flow rate of 4.0–5.0 mL/s followed by a 40-mL saline flush using a mechanical dual power injector. For optimal intraluminal contrast enhancement, the automatic bolus-tracking technique had the region of interest located at the level of the main pulmonary artery with a trigger threshold of 120 HU. Images were reconstructed with a thickness of 1 mm and an increment of 1 mm or 1.25 mm. The imaging data were transmitted to a post-processing workstation for multi-planar reconstruction and picture archiving and communication systems.

CTPA image analysis

All CTPA images were reviewed by a senior radiologist (Dr Emilia, principal COVID CT thorax analyst with 6 years'' experience). The CTPA images were analysed using mediastinal window setting (width, 350 HU; level, 50 HU). The lung window was set with a width of 1500 HU and level of –500 HU. The anatomical sites of the acute pulmonary

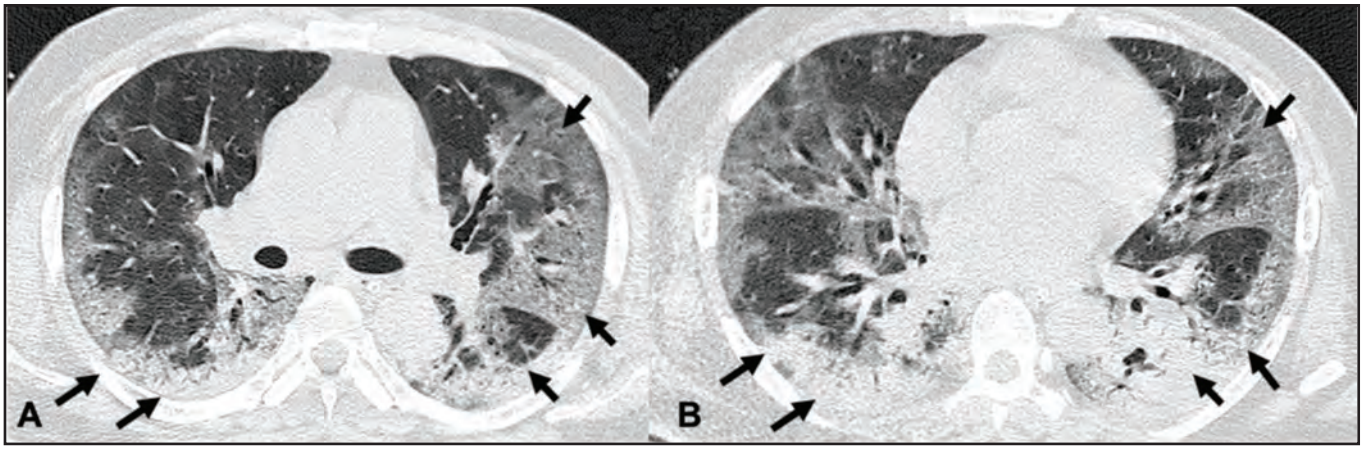

Fig. 1: Computed tomography (CT) pulmonary angiography: A and B: Axial CT images in lung reconstructions at mid and lower lung levels showing typical COVID-19 lesions with bilateral patchy ground-glass opacities and consolidations in predominantly peripheral distribution (black arrows). The pulmonary involvement of COVID-19 lesions was 50% of lung volume.

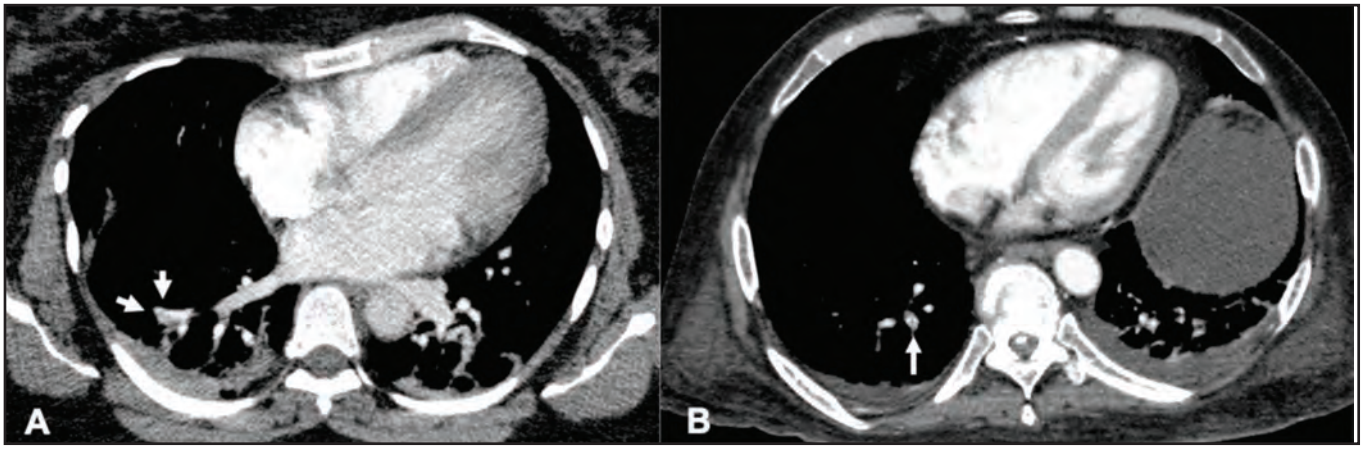

Fig. 2: Computed tomography (CT) pulmonary angiography: A and B: Axial CT images in thin slice demonstrating presence of thrombi (white arrows) in the subsegmental branches of right descending pulmonary artery in different patients with category 4 COVID-19 infection.

thromboembolism were recorded based on the most proximal anatomic location. For each PTE location, the degrees of lung involvement were documented as multi-lobar (unilateral), multi-lobar (bilateral) or single-lobar (unilateral). In addition, the severity of COVID-19 pneumonia and organising pneumonia changes were reported based on the total areas of pulmonary involvement. We divided the aforementioned severity into four categories based on the extent of pneumonia changes detected on CT images at lung window: (1) minimal (<25%), (2) mild (25–50%), (3) moderate (51–75%), and (4) severe (>75%), which was adapted and modified from Pan et al.[9]

Statistical Analysis

The data obtained were analysed using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp.). Demographic data, clinical data, laboratory data and radiological data were presented descriptively. Categorical variables between cases with PTE disease and cases without PTE disease were compared using Pearson Chi-Square or Fisher's Exact test whilst continuous variables were compared using independent t-test or Mann–Whitney U test. For all statistical comparisons, a p value of < 0.05 would be deemed significant.

RESULTS

Clinical Characteristics of COVID-19 Patients with Suspected PTE

A total of 184 COVID-19 patients with suspected PTE who had undergone CTPA were included in this study, and they were further divided into PTE and non-PTE cohorts based on the CTPA findings. Intriguingly, there was a preponderance of PTE among the study populations with a prevalence rate of 81.5% (150 vs. 34).

A review of the clinical characteristics demonstrated that gender distribution was relatively similar between PTE and non-PTE cohorts with a male predominance (60.7% vs. 61.8%, p=0.906). Further, the PTE cohort was significantly elder compared the non-PTE cohort (mean age in years 57 vs. 49; p=0.002). The commonest comorbidities observed were diabetes mellitus (n=95, 51.6%) and hypertension (n=80, 43.5%), which occurred in approximately half of the study population. Also, the prevalence of dyslipidaemia (16.7% vs. 8.8%; p=0.250) and ischaemic heart disease (11.3% vs. 5.9%;

p=0.534) were higher in the PTE cohort although this was not statistically significant. Notably, none of the PTE cohort had clinical deep vein thrombosis.

Almost all of our patients were symptomatic at presentation (n=183, 99.5%), and a wide range of symptoms were reported. There was no significant difference between PTE and non-PTE cohorts in terms of symptoms at presentation. The commonest symptoms documented were cough (n=143, 77.7%), fever (n=129, 70.1%), shortness of breath (n=124, 67.4%), diarrhoea (n=57, 31.0%) and fatigue (n=37, 20.1%). In contrast, anosmia (n=8, 4.3%) and ageusia (n=8, 4.3%) were rarely reported. The median temperature at presentation was 37.9° C (IQR: 37.0–38.7).

Based on the COVID-19 day of illness analysis, the median day of illness at presentation was 5 days (IQR: 4.0–7.0) whilst the median day of illness during CTPA was 10 days (IQR 8.0-13.0). Noticeably, the PTE cohort was generally more severe in contrast to non-PTE cohort as evidence by the former cohort had higher prevalence in more advanced categories with *p* value 0.042. The PTE cohort reported a higher percentage of category 5a (20.0% vs. 11.8%) and category 5b (18.0% vs. 5.9%). On the other hand, category 2 (5.9% vs. 0.7%), category 3 (5.9% vs. 1.3%), category 4a (41.1% vs. 37.3%) and category 4b (29.4% vs. 22.7%) predominantly occurred among the non-PTE cohort.

Interestingly, virtually all subjects received steroidal treatment during/prior to CPTA (n=180, 97.8%.). Conversely, not all subjects received anticoagulation therapy during/prior to CTPA and this was predominantly observed among non-PTE cohort (14.7% vs. 4.0%) despite the suspicion of PTE. Additionally, the percentage of immunomodulator (20.6% vs. 38.7%; *p*=0.046) and favipiravir (52.9% vs. 74.0%; *p*=0.015) therapy were also significantly lower among the non-PTE cohort indicating a milder severity. Moreover, the oxygen requirement also varied between PTE and non-PTE cohort, especially the usage of mechanical ventilatory support (27.3% vs 8.8%; *p*=0.022).

Lastly, the PTE cohort was generally more ill as indicated by a higher proportion of them requiring inotropic support during/prior to CTPA (15.3% vs. 2.9%; *p*=0.086) as well as throughout admission (22.7% vs. 5.9%; *p*=0.026). Despite the absence of a significant difference in intensive care unit (ICU) admission rate (48.0% vs. 35.3%; *p*=0.179), the length of both ICU stays (median number of days 8 vs. 3; *p*=0.021) and hospital stay (median number of days 14.5 vs. 12; *p*=0.006) were significantly longer among PTE cohort. The beforementioned observations translated into a higher proportion of in-hospital death (14.0% vs. 2.9%; *p*=0.083) and 60-day all-cause fatality (14.7% vs. 2.9%; *p*=0.083) among them, though this was not statistically significant (Table I).

Laboratory Data of COVID-19 Patients with Suspected PTE

Analysis of the laboratory parameters showed that the median level of all full blood count parameters at admission was within normal range, except absolute lymphocyte count which was relatively low (median 1.0; IQR 0.7–1.4). Peak C-reactive protein (CRP) (median 124.1 vs. 82.1; *p*=0.027) and ferritin level (median 1469 vs. 1229; *p*=0.024) were significantly higher among the PTE cohort. Other laboratory results including peak serum aspartate transaminase (median 73 vs. 59.5; *p*=0.077), alanine transaminase (median 92 vs. 78; *p*=0.202) and creatinine levels (median 97 vs. 94.3; *p*=0.366) were generally higher among PTE cohort but statistically not significant. Higher peak procalcitonin level (*p*=0.171) and peak D-dimer (*p*=0.242) were noted among PTE cohort as well. Intriguingly, seven PTE patients (4.7%) had a negative D-dimer test and conversely, 31 non-PTE patients (91.2%) recorded a positive D-dimer test. Further, the D-dimer levels from two subjects in the later were raised out of proportion (>20.0 µg/ml) despite the absence of PTE disease. Overall, no significant differences were found between PTE and non-PTE cohort, except peak CRP and ferritin levels(Table II).

Radiological Features of COVID-19 Patients with Suspected PTE

Comparison of the radiological features indicated that the patterns of COVID-19 pneumonia/organising pneumonia changes were significantly more extensive among the PTE cohort with *p*<0.001. For example, the description of moderate (37.3% vs. 20.6%) and severe changes (26.7% vs. 5.9%) was noticeably higher among them (Figure 1). In contrast, mild (41.2% vs. 32.0%) and minimal areas (29.4% vs. 4.0%) of involvement were primarily observed among the non-PTE cohort. Besides, the percentage of pulmonary angiopathy changes was also significantly elevated among PTE cohort (33.3% vs. 2.9%). A myriad of non-COVID pneumonia related radiological changes was also observed, especially among the PTE cohort (50.7% vs. 14.7%)

In the PTE cohort, the thrombotic lesions were mainly located in the peripheral pulmonary arteries, with the most proximal anatomical location restricted to the segmental arteries in 3 patients (2.0%) and in subsegmental arteries in 147 patients (98.0%) (Figure 2). The degree of PTE involvements occurred in single lobar, unilateral among 53 subjects (35.4%), multilobar, unilateral among 2 subjects (1.3%) and multilobar, bilateral among 95 subjects (63.3%) (Table III).

DISCUSSION

Immunothrombosis, which was promulgated during COVID-19 pandemic expounds a distinct pathophysiological pathway for PTE disease associated with COVID-19 infection.[10] In essence, it implicates that dysregulated host immune activation as the primary mechanism for the widespread pulmonary endothelial injury and hypercoagulable state, which would lead to in situ pulmonary thrombosis. This hypothesis is in keeping with the published COVID-19 post-mortem case series, which reported the presence of widespread pulmonary microthrombosis among the deceased.[11,12]

The results derived from this study concurred with the above idea that COVID-19-associated thrombosis primarily occurs due to in situ immunothrombosis. Firstly, none of our PTE cohort had clinical deep vein thrombosis. Furthermore, hyperinflammatory activities appeared to be more rigorous among the PTE cohort as suggested by the disproportionately higher CRP and ferritin values. It is also noteworthy that the thrombosis exclusively affected the subsegmental and segmental as well as peripheral bronchial arteries branches

only, which differs from the conventional embolism-associated PTE described in the non-COVID populations.[13] Moreover, the more extensive involvement of COVID-19 pneumonic changes and existence of microangiopathy support the notion that the thrombosis occurred as result of pulmonary vasculature endothelial damage.

CT patterns in our PTE cohort bear close resemblance to the previously published works in numerous aspects.[14,15] The foremost similarity is that virtually all the existing literature describes that thrombosis in COVID-19 shows a predilection for the peripheral and smaller pulmonary arteries. Another common finding is that the sites of thrombosis highly correlate with lung parenchyma which is affected by COVID-19 disease. In this study, we also reported a high prevalence of microangiopathic changes among the PTE cohort. Collectively, these findings strengthen our belief that PTE disease in COVID-19 represents a unique thrombotic phenotype driven by immunothrombosis that should fuel further studies on its pathophysiology.

Admittedly, the number of non-PTE cohort in this study was inadequate to perform multivariate analysis in identifying the risk factors associated with PTE. Nonetheless, we have identified several notable laboratory and radiological features that are highly associated with PTE as mentioned above. To note, the D-dimer value was proven to be not an ideal biomarker in predicting PTE disease as it lacks specificity. Additionally, we did not find discernible symptoms between the two groups. Considering all these, we recommend that suspicion of PTE disease among COVID-19 patients should be based on patient clinical conditions, especially those with rapid respiratory deterioration, unexplained tachycardia, haemodynamic instability or moderate to extensive COVID-19 pneumonic X-ray changes.[4,16]

The landscape of COVID-19 therapy is an evolving field and several medications such as the usage of hydroxychloroquine and favipiravir had become obsolete through the course of time. At present, antiviral, anticoagulant, steroidal and immunomodulator therapies remain to be the cornerstone of treatment still as most complications arise from the prothrombotic state and immune hyperactivation.[8,17] It is evident that almost all the PTE subjects had received ongoing anticoagulant and steroidal treatment prior to CTPA examination. Hence, it is logical to hypothesise that most subjects developed the PTE disease either from the outset or during the course of treatment. Also, treatments mentioned before appeared to be only capable of ameliorating the propagation or progression of the existing thrombosis at best. In our opinion, the most efficacious PTE disease prevention strategy remains to be effective immunisation or timely administration of a potent antiviral or immunomodulator which could circumvent pulmonary vasculature injury caused by the cytokine storm.

To date, notable heterogeneity exists in regard to the study design among the published prevalence study examining PTE disease associated with COVID-19 infection.[5] As a corollary, there exists a large variation in the global PTE disease incidence rate. For instance, Leonard-Lorant et al reported an incidence rate of 30% among the COVID-19 cohort with the suspicion of PTE; whilst Scudiero et al reported an incidence rate of 14% among the COVID-19 cohort with the suspicion of PTE.[3,18] Interestingly, despite the similarity in recruiting both ICU and non-ICU patients in the study, our study recorded a comparatively higher incidence of PTE disease. We postulate that this disparity could arise from the difference in the COVID-19 variant that was ubiquitous during the study time frame as well the study population clinical profiles. It is noteworthy that approximately half of our PTE cohort required ICU admission. Notwithstanding, PTE disease was proven to be a formidable disease as those inflicted with it were generally more ill and reported a higher ICU admission rate as well as fatality rate.

A few limitations exist in this study. Firstly, we would like to cautiously remind the readers that the study population was from the pre-vaccination era, and also, they were infected with the most virulent Delta (B.1.617.2) strain during the course of illness. As well, the CT images were analysed by only a single radiologist. Therefore, the interrater reliability or agreement could not be determined though that is not our study objective. Lastly, the level of important proinflammatory mediators, like serum interleukin and interferon levels, were not measured due to unavailability such test in our centre. Nevertheless, this paper provides a comprehensive review including both ICU and non-ICU COVID-19 patients with suspected PTE disease. Moreover, it also compares and contrasts the important clinical, laboratory and radiological aspects of both PTE and non-PTE cohorts with COVID-19 infection.

CONCLUSION

Our data suggest that PTE disease was common among COVID-19 patients and its' phenotype is different from the conventional PTE disease among patients without COVID-19 infection. Further, the presence of marked hyperinflammatory activities, unique thrombotic lesion sites and concomitant moderate to severe COVID pneumonia substantiate immunothrombosis as the likely cause. Absence of telltale symptoms or biomarkers suggests that the decision to investigate PTE disease should be based on the patient clinical conditions. Lastly, it is hoped that similar research will be undertaken among our post-vaccination populations in order to advance our understanding towards this area.

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ETHICAL APPROVAL

This study was registered with National Medical Research Register and approved by the Medical Research and Ethics Committee of the Ministry of Health. MREC Approval Letter: KKM/NIHSEC/P21-1574(11)

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Filling of the resultant cavity after curettage of benign bone tumours is still controversial

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ABSTRACT

Introduction: Benign bone tumours occur most commonly during the first through third decades of life and often weaken the bones, which may predispose them to pathological fractures. Great diversity and debate in the management of primary bone tumours are based on the tumour extent. There has been an increasing trend toward the intra-operative filling of these lesions. We hypothesised that in some benign bone tumours, filling the resulting cavity after curettage was unnecessary. This study was carried out to determine whether it is necessary to fill the resultant cavity after the curettage of benign bone tumours and to represent various fillers.

Materials and Methods: A retrospective study of patients diagnosed as benign bone tumours according to the Enneking classification who underwent simple or extended curettage at Menoufia university-Orthopedic Oncology Division (with or without grafting or filling) during the surgical treatment (Jan 2015 to Feb 2020). A review of the medical records was done. Lesions' size (length, width and depth) was measured on plain radiographs using the image j program. When applicable, degrees of filling of the resultant cavity were classified into four categories, according to Modified Neer's classification. Functional evaluation using the musculoskeletal tumour society (MSTS) score was reviewed.

Results: Overall, 88 patients diagnosed with a primary bone tumour and who received the surgical intervention were included in the study. The mean age of the patients was 22.61+13.497 (3–58) years. There were 48 males and 40 females (54 right and 34 left). The mean follow-up period was 28.09+16.13 months. The most common location was the distal femur in 15 patients, the proximal femur in 10 patients and the proximal tibia in 12 patients. The most common diagnosis was giant cell tumour in 20 patients, followed by UBC in 19 patients, ABC in 15 patients and enchondroma in 13 patients. Twenty-three patients had simple curettage, while 65 patients had extended curettage. Mean MSTS was 28.78±1.68. Fifty-five lesions were classified according to modified Neer's classification.Thirtty-two patients were classified as type 1 with complete healing,22 patient was classified as type 2 with partial healing, and only one was classified as a recurrent lesion. Seven patients (7.9%) developed local recurrences.

Conclusion: Filling the resulting cavity after the removal of the pathological tissues is usually necessary but not always required. This is determined by the type of lesion and the size of the resulting cavity following curettage. Individualised surgery is required; additional fixation should be considered.

KEYWORDS:
Enneking, benign bone tumours, filler, surgical interventions, extended curettage, Giant cell tumour simple bone cyst, non-ossifying fibroma

INTRODUCTION

Benign bone tumours occur most commonly during the first through third decades of life and often weaken the bones, which may predispose them to pathological fractures.[1–3] Benign lytic bone lesions, such as simple bone cyst, non-ossifying fibroma and fibrous dysplasia are asymptomatic, most often affect younger individuals, and these typically stabilise or resolve after skeletal maturity. Because of this, surgery usually is not required unless the lesion's size may cause a pathological fracture, at which point curettage with or without grafting is the preferred treatment to prevent complications.[1,4]

The surgical intervention is controversial and varies according to the anatomic site. The goal is to prevent tumour recurrence, allow the restoration of bone strength and fix fractures already has occurred. Larger lesions need to be filled to decrease the risk of pathological fractures. Thus, filling the bone defects after tumour curettage is currently the most popular approach.[1,5]

Large bone cavities have been reinforced with autologous bone grafts, allografts, bone cement and bone substitutes.[4,6–9] Autologous grafts have an ideal success rate, low risk of disease transmission and histocompatibility; however, there is limited availability and donor site morbidity, especially in children.[10,11] Allografts carry a risk of infection, causing restriction of their use in filling bone cavities, particularly in children, and are no longer used widely as autografts.[12] Calcium phosphate ceramics act as osteoconductive filler of bone defects that completely resorb as newly formed bone remodels and restores structural properties.[13] Many bone substitutes aim to fill these defects,[8] yet there is little evidence

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for their efficacy. There have been very few comparisons with the normal degree of healing expected in bone.[4,14]

Bone cement has been an alternative to the costly allograft and has widely been compared against allografts.[15] It has been studied previously with good results and is the procedure of choice for lesions associated with large defects.[16] Another technique in which cement is added to autograft or allograft also can provide mechanical stability.[17]

Great diversity and debate in the management of primary bone tumours are based on the tumour extent. There has been an increasing trend toward the intraoperative filling of these lesions, especially those in weight-bearing areas.[3,5,6,16-19] The optimal treatment and filling material for these lesions are currently unknown.[19] Currently filling of the cavity is still debatable based on the size of the cavity, availability of filler, cost-effectiveness, and morbidity of autograft harvest, when summated together the decision is determined intraoperatively and surgery is individualised to every patient.[20-22]

We hypothesised that in some benign bone tumours, filling the resulting cavity after curettage was unnecessary. This study was carried out to determine whether it is necessary to fill the resultant cavity after the curettage of benign bone tumours and to represent various fillers.

MATERIALS AND METHODS

This is a retrospective study of patients with benign bone tumours who underwent surgical treatment. The study was conducted after the approval of the institutional review board of Menoufia university and written informed consent from patients. Patients diagnosed as benign bone tumours according to the Enneking classification[23] who underwent simple or extended curettage (with or without grafting or filling) during the surgical treatment, operated between Jan 2015 and Feb 2020 with a minimum follow-up of 1 year were included in the study. Surgeries were conducted by two senior orthopaedic surgeons (ITB&BZ), both orthopaedic consultants at the orthopedic oncology division (Menoufia University, Faculty of Medicine, Orthopedic Department) which is one of the tertiary referral centres of tumour patients in Egypt. Patients with a benign tumour in the axial skeleton, tumour-like condition or grade one chondrosarcoma and who underwent curettage were excluded. Patients who received a local injection, radiofrequency ablation or had no surgical interventionand patients with lost follow-up were excluded.

A review of the medical records of the patients was done. Data collection, extraction and analysis were done by orthopedic surgeons mainly (BAH&AOE), And all radiological parameters were reviewed together with a consultant radiologist (MMM). The collected data included history and physical examination, demographic data, radiological evaluation (pre-operative and post-operative radiographs, CT and MRI if available), tumour diagnosis that was confirmed histologically postoperatively, site of the lesion type and cause of surgical intervention, methods of fixation if used, type of curettage either simple or extended using a high-speed burr, method of filling of the resultant cavity if done, complications, need of reoperation, any recurrence. Functional evaluation using the musculoskeletal tumour society (MSTS) score was also reviewed.

Magnetic resonance (n=56) and computed tomography images (n=25) were revised to see the intraosseous extent and involvement of soft tissue or articular surface. Pre-operative biopsy (n=43) was performed on all locally aggressive lesions (GCT, ABC). Most of the lesions with characteristic radiographic features, for example, non-ossifying fibroma, simple bone cysts, fibrous dysplasia, and enchondromas in the hand, were treated based on radiological appearances.

Curettage was performed through a wide cortical window to give complete exposure to the lesion. The tumour tissue was removed using varied sizes of curettes, further extension using high-speed burr together with lavage of the cavity to dislodge the remaining tumour tissue, and the adjuvant and /or filler was used.

Lesions' size (length, width and depth) was measured on plain radiographs. For those with pathological fractures, measurements were done on immediate post-operative radiographs. Measurements of the lesion length and width were done on anteroposterior radiographs, and the depth of the lesion was measured in lateral view using the widest diameter. Measurements were done on calibrated images using the image j program.

According to Modified Neer's classification, the degrees of filling of the resultant cavity were divided into four groups where relevant.[24,25] based on the final post-operative radiographs.Modified Neer classification of radiological evaluation of bone defect healing includesgrade I (Complete Healing) representingcomplete or almost complete filling of the initial lesion with radiological evidence of new bone formation, grade II (Partial Healing) representingincomplete healing and/or graft resorption in an area(s) less than 50% of the initial lesion with enough cortical thickness to prevent fracture, grade III (Persistent Lesion) represent Graft resorption or persistent radiolucent area (s) greater than 50% of the initial lesion and/or with a thin cortical rim potentially at risk for fracture, and grade IV (recurrent lesion) represent progressive lesion reappeared in a previously obliterated area or a residual radiolucent area verified by biopsy.

Statistical Analysis

For statistical analysis, IBM SPSS version 25.0 (SPSS Inc., Armonk, NY) was employed. When appropriate, categorical variables were compared using the Chi-square or Fisher's exact tests. When suitable, continuous variables were compared using the Student's t-test or one-way ANOVA. A p-value of less than 0.05 was used to determine statistical significance.

RESULTS

Overall, 88 patients were diagnosed with a primary bone tumour and received surgical intervention. The mean age of the patients was 22.61+13.497 (3–58) years. Thirty-nine patients (44.3%) were skeletally immature (under 16 years of

age) at the time of treatment. There were 48 males and 40 females. The side of the lesion was right in 54 patients and left in 34 patients. The mean follow-up period was 28.09+16.13 months. Only three patients were presented with previous surgical interventions considered as recurrent lesions, while the others had no previous surgery. The main presentation of the patients was pain, swelling, limping and pathological fractures. Twenty-seven patients (30.7%) presented with pathological fractures (Table I).

Fifty-seven lesions were in the lower extremity, with two lesions located at the posterior acetabular column and superior pubic rami, while 31 lesions were in the upper extremity.

The most common location of the lesions was the distal femur in 15 patients (17%), the proximal femur in 10 patients (11.4%), the proximal tibia in 12 patients (13.6%), the phalanges in 12 patients (13.6%), the proximal humerus in 6 patients (6.8%), the distal tibia in 5 patients (5.7%), three affections fore each(calcaneus, femur mid shaft, metacarpal bone, proximal radius,tibia mid shaft), two affections for each (humerus mid shaft,superior pubic ramus,scapula), and one affection for the remaining (acetabulum posterior column, distal fibula, distal humerus,distal radius,metatarsal bone, proximal ulna). CT was available for 25 patients, while MRI was available for 56 patients.

The most common diagnosis was giant cell tumour in 20 patients (22.7%), followed by UBC in 19 patients (21.6%), ABC in 15 patients (17%), enchondroma in 13 patients (14.8%), NOF in 6 patients (6.8%), chondroblastoma in 4 patients (4.5%), osteoblastoma in 4 patients (4.5%), osteoid osteoma in 3 patients (3.4%), FD in 3 patients (3.4%), desmoplastic fibroma in one patient (Figures 1–3).

Twenty-three patients had simple curettage, while 65 patients had extended curettage. A high-speed burr was used in 68 patients. Extended curettage surgery involved intralesional curettage through a generous cortical window followed by burring, cleansing, and lavage of the lesion. Following surgery, each cavity was either left empty with no filler or filled with autologous bone graft, bone substitute, or bone cement. Forty-two patients had no filling of the defect while the other 46 were packed by either autologous bone graft (10 patients), bone substitute (3 patients), or bone cement (33 patients). Thirty-five patients had fracture fixation or lesion augmentation.

For lower extremity lesions, depending on the size of the lesion and the radiological features, partial weight-bearing was allowed before reaching full weight-bearing. For upper extremity lesions, immobilisation is followed by the resumption of activities based on lesion consolidation.

The mean length of the lesions was 39.23±22.78 mm, the mean width was 25.19±12.18mm, and the mean depth was 21.86±10.87mm. Only 17/27 fractures required fixation, while the remaining was splinted or received bone cement to augment the lesions.

The mean MSTS was 28.78±1.68, there was no statistical significance between those who received filling and those who did not (*p*-value= 0.127) and also no statistical difference between the different fillers used regards the MSTS (*p*-value=0.227)

As the healing and lesion consolidation cannot be evaluated in patients receiving bone cement as a filler, a review of serial radiographs showed 55 lesions were not filled by bone cement and were classified according to modified Neer's classification.Thirty-twopatients were classified as type 1 with complete healing of the lesions,[22] patients were classified as type 2 with partial healing of the lesions, and only one lesion was classified as a recurrent lesion (type 4). The filling pattern began with cortex thickening, followed by the appearance of bone septate through the defect, which progressed to either complete or partial filling of the lesion.

Non-significant relation between the different studied variables and filling of resultant cavity p-value for different variables was (side 0.438, gender 0.096, pathological fracture 0.013,presentation as primary or recurrent 0.646, centricity of the lesion 0.048, use of high-speed burr 0.03,complications 0.374, MSTS 0.127). Only more tendency to non-filling in skeletally immature patients(p-value˃0.005)

Lesions that were filled with bone graft or bone substitute showed the same healing potential as those that were not filled. However, there was no significant relationship between the type of lesion and choice of filling and the healing of the lesion regarding modified Neer's classification p-value = 0.419 (Table II).

Regarding the filling of different lesions, there was a tendency to non-filling of lesions such as enchondroma due to small defects, also in lesions with high potential of bone healing such as NOF and UBC (Table III).

Lesions were evaluated during and after curettage, and if there was still enough strength after the procedure, the decision of non-filling was made, taking into account the lesion size in relation to the affected bone and donor site morbidity, especially in young patients.

Seven patients (7.9%) developed local recurrences during the follow-up period; 4 lesions were UBC, 2 lesions were ABC, and 1 lesion was a desmoplastic fibroma. All patients were controlled by repeated curettage, extending it using a high-speed burr. Only one patient had two recurrences (Figure 1). No case had post-operative wound infection.

During follow-up, two patients had osteoarthritic changes (GCT proximal tibia, GCT distal femur) with occasional pain that responded to conservative measures, three patients had occasional pain and one of these had lower limb edoema, all responded to conservative measures, one patient hadSubdeck's atrophy and mild deformity, the pain was controlled, and range of motion and daily activity was restored fully.

Table I: Patient characteristics, demographic data, diagnoses and treatment outcome

	no	%		no		%
Side			**Type of filling**			
Left	34	38.6	Autograft	10		11.4
Right	54	61.4	Bone cement	33		37.5
Gender			Bone substitute	3		3.4
Female	40	45.5	No filling	42		47.7
Male	48	54.5	**Modified Neer's classification**			
Skeletal maturity status			Not applied	33		37.5
Immature	39	44.3	Complete healing	32		36.4
Mature	49	55.7	Partial healing	22		25.0
Pathological fractures			Recurrent cyst	1		1.1
NO	61	69.3	Curettage			
Yes	27	30.7	Extended	65		73.9
Extremity affection			**Simple**	23		26.1
Lower limb	57	64.7	Duration of symptoms (months) Mean±SD	3.90±4.29		
Upper limb	31	35.2	MSTS(Mean±SD)	28.78±1.68		
Lesion presentation			**Measurements**	Total(n=88)	UE(n=31)	LE(n=57)
Primary	85	96.6	Lesion maximum length in mm (Mean±SD)	39.23±22.8	34±21.61	42±23.3
Recurrent	3	3.4	Lesion maximum width in mm (Mean±SD)	25.19±12.18	18.65±9.3	28.8±12.3
			Lesion maximum depth in mm (Mean±SD)	21.86±10.87	16.19±8.5	25.1±10.8

Table II: Distribution of lesions regards Modified Neer's classification compared to the type of filling

Modified Neer's classification		filling or not			Total
		Filling with BG or BS	no filling	Bone cement	
Complete healing	ABC	2	3		5
	Chondroblastoma	0	2		2
	Enchondroma	1	8		9
	GCT	0	1		1
	NOF	1	2		3
	Osteoblastoma	1	0		1
	Osteoid Osteoma	0	3		3
	UBC	2	6		8
	Total	7	25		32
Recurrent cyst	UBC	1			1
Bone cement	ABC			4	4
	Chondroblastoma			2	2
	Enchondroma			1	1
	FD			3	3
	GCT			19	19
	osteoblastoma			1	1
	Osteoblastoma			2	2
	UBC			1	1
	Total			33	33
Partial healing	ABC	4	2		6
	Dysmoblastic fibroma	0	1		1
	Enchondroma	1	2		3
	NOF	0	3		3
	UBC	0	9		9
	Total	5	17		22
Total	ABC	6	5	4	15
	Chondroblastoma	0	2	2	4
	Dysmoblastic fibroma	0	1	0	1
	Enchondroma	2	10	1	13
	FD	0	0	3	3
	GCT	0	1	19	20
	NOF	1	5	0	6
	osteoblastoma	0	0	1	1
	Osteoblastoma	1	0	2	3
	Osteoid Osteoma	0	3	0	3
	UBC	3	15	1	19
	Total	13	42	33	88

Table III: Different histological diagnoses and their filling and the mean volume of the lesions

	Filling with bone graft or bone substitute		No filling		Filling with bone cement		Total
	NO	Mean volume (CM3)	NO	Mean volume (CM3)	NO	Mean volume (CM3)	
UBC	3	18.8	15	19.4	1	72	19
Enchondroma	2	0.92	10	2.1	1	22.5	13
ABC	6	19	5	34	4	21.6	15
NOF	1	23.8	5	6.7	0	-	6
Osteoid Osteoma	0	-	3	55	0	-	3
Chondroblastoma	0	-	2	7.25	2	20.4	4
Osteoblastoma	1	8	0	-	3	6	4
FD	0	-	0	-	3	104	3
Desmoplastic fibroma	0	-	1	24.5	0	-	1
GCT	0	-	1	1.5	19	89	20
Total	13	15.7	42	17	33	68	88

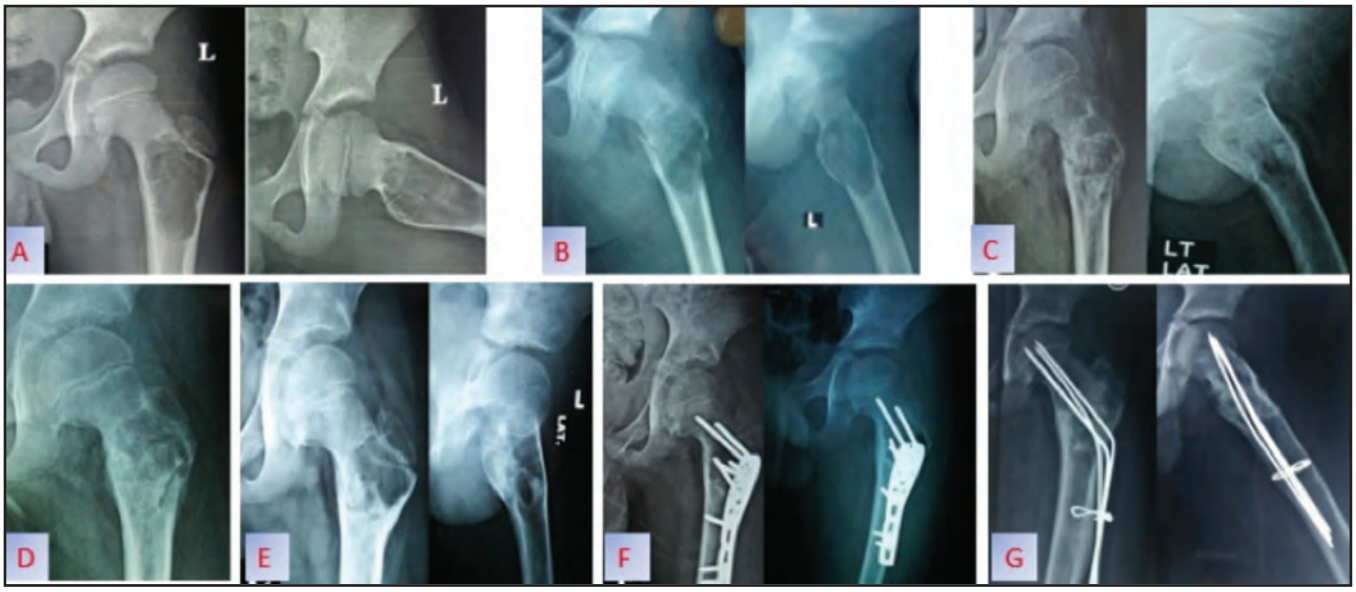

Fig. 1: Male patient 11 years old presented with a unicameral bone cyst of the proximal femur (A), underwent curettage-only surgery and spica cast (B), 3weeks post-operative had a pathological fracture spica cast was applied until the consolidation of the cyst wall (C, D) but with a persistent cyst, after 4 months follow-up (E), re-curettage and plate augmentation was done, but with cyst persistence (F), 6months after the second intervention, extended curettage using a high-speed burr and lesion augmentation with Wagner technique was done with full consolidation of the lesion after 14 months follow-up (G)

DISCUSSION

Benign bone tumours may be found incidentally on imaging for other causes and can present with mild pain and localised swelling.[1] Curettage, alone or in combination with grafting, can relieve pain and reach 95% cure rates in various forms of benign bone tumours.[1,26-28] Whether or not adjuvants are employed, adequate exposure and careful curettage are required to maximise local control.[29] Depending on the tumour diagnosis, the overall recurrence rates can vary significantly.[30] Recurrence rates in giant cell tumours treated with curettage and adjuvant filling have ranged from 7 to 50%, despite numerous attempts to lower this probability of local recurrence, including the use of adjuvants such as phenol, cryotherapy and bone cement.[9,31,32]

The use of bone cement was preferred as a filler for the defect and structural support, also giving benefit through its exothermic property on residual tumour cells. Concern, when used near the surface of a joint, may cause thermal injury and damage to the chondrocyte leading to secondary osteoarthritis.[4,10,16,30] The use of a high-speed burr and adjuvants such as (hydrogen peroxide, alcohol, and the thermal energy of bone cement when used) to extend the destruction of residual tumour cells resulted in a low recurrence rate in this series.

Mechanical insufficiency or microfractures can cause pain in benign lytic bone lesions, which can indicate people are at risk of pathological fracture.[33-35] Shih et al. and Drennan et al. used curettage and grafting along with internal fixation for patients with active lesions of the lower extremity.[35,36] Moretti et al. reported that curettage and grafting of symptomatic benign lytic bone lesions provide adequate mechanical stability and allow a return to full painless activity.[1]

In benign aggressive bone lesions, chemical adjuvants such as phenol, hydrogen peroxide and alcohol have been utilised to expand the curettage margin, minimising recurrence and necrosis.[37,38] Pathological fractures following a benign tumour are not a contraindication to treatment by curettage and cementation.[16,39]

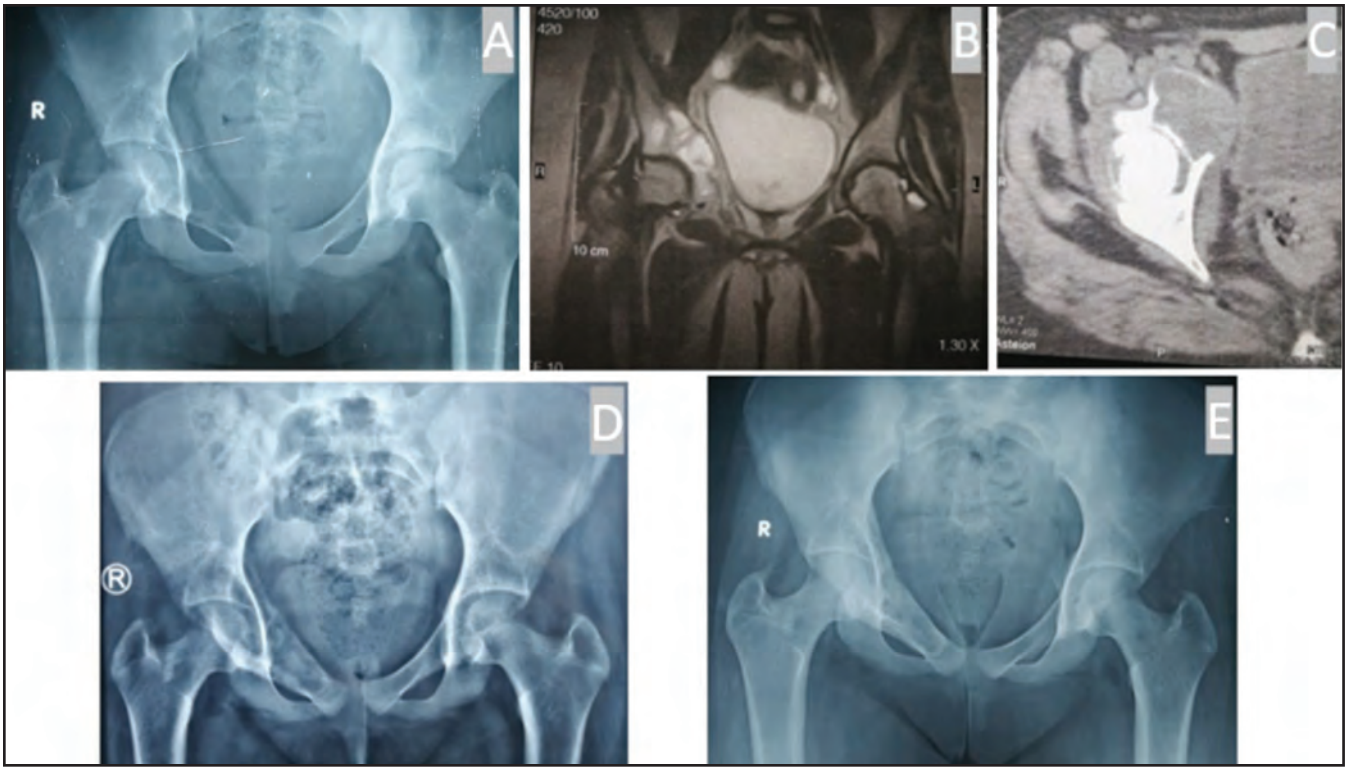

Fig. 2: Female patient presented with ABC of the right superior pubic ramus, (A) Plain radiographs with extensive affection of the right pubic ramus. (B, C) MRI images with multiple fluid-fluid levels, (D) Plain radiograph 2months follow-up after extended curettage surgery using high-speed burr, (E) Follow-up radiographs after 12 months with full consolidation of the lesion

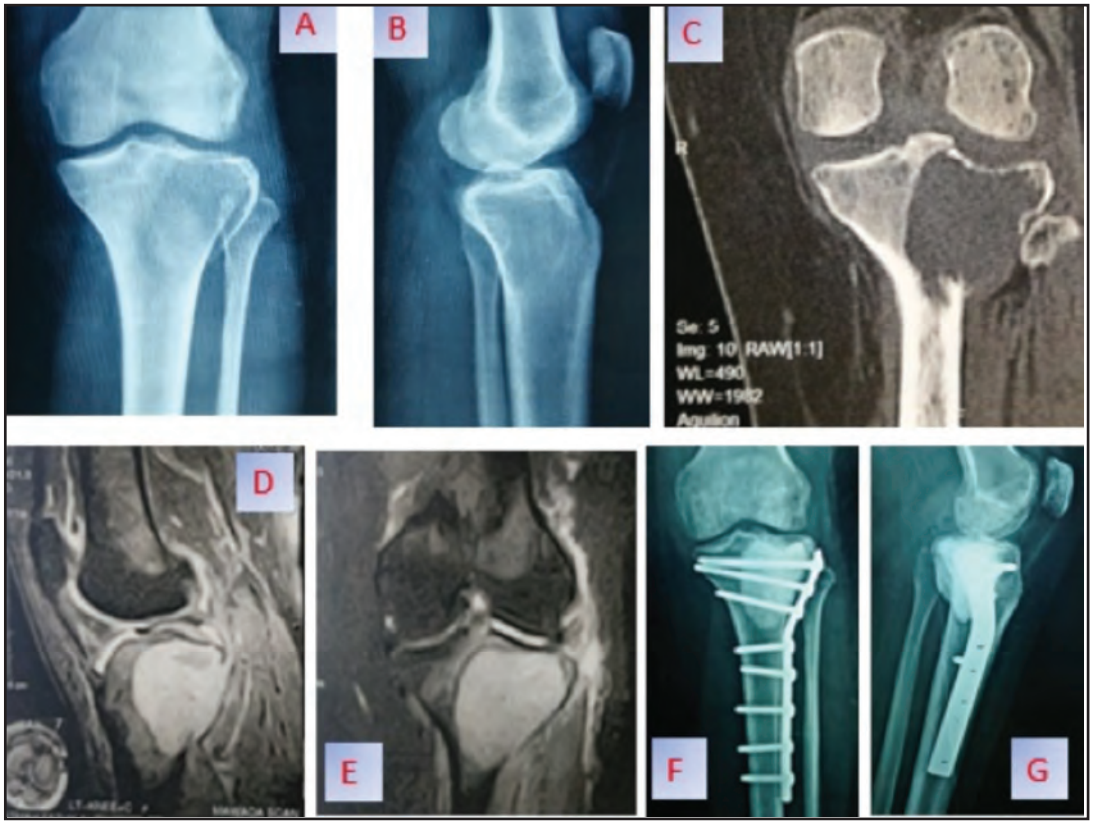

Fig. 3: Female patient 30 years old presented with GCT with pathological fracture, (A, B) plain radiographs with lytic lesion affecting the proximal tibia approaching articular cartilage, (C) CT image with extensive lesion broaching the cortex with pathological fracture. (D, E) MRI images with high signal intensity in T2 images with an expansion of the posterior cortex. (F, G) plain radiographs after extended curettage of the lesion using high-speed burr and cementation and plate osteosynthesis after 2 years follow-up

Wu et al. retrospectively assessed 84 patients with simple bone cysts who had undergone curettage and filling of the bone defects with grafts. Only two of all variables evaluated were significantly correlated with the prognosis: tumour location and tumour length, those at the proximal femur were significantly more likely to achieve complete healing (Neer I). Post-operative re-fracture occurred in one case.[2] Internal fixation was used to supplement fracture fixation or lesion augmentation in 35 patients with defects that may predispose them to a significant risk of fracture.

Most benign bone lesions had a natural tendency to fill the resultant defect following curettage, also filling the defect improves the chances of local control and also had a strong capacity to create new bone after trauma or haematoma created after curettage;there have been some studies reporting on the ability of a surgically created bone defect to fill in if left empty.[4–7,17,38,40,41] Filling of the resultant cavity after curettage was based initially on the lesion size and the ability of these cavities to fill without filling. Minor defects can be left empty. While in large defects, especially those after curettage of GCT filling with bone cement were always considered, as there is a risk of fracture or collapse of the joint surface if the cavity is left with no filling.

The size of the lesion, donor site morbidity of the graft, and type of lesion were the most important factors in the filling and type of filling. Smaller lesions and lesions such as NOFs, enchondromas, and UBCs had a higher likelihood of not filling, which could be attributed to the possibility of bone healing.

Kundu et al. reported that 42 patients with benign bone tumours underwent curettage without grafting or filling of the defect by any other bone substitute. They reported that there is a natural healing ability of bone without filling. In selected sizes and locations of benign lytic tumours and tumour-like lesions, extended curettage alone can be sufficient.[4]

Obtaining a large amount of autograft is quite a large operative procedure, which is likely to lead to significant morbidity.[10] There may be a reluctance to use an allograft; however, particularly in children or young people. Bone substitutes have become more popular with unlimited supply, particularly in defects of large size but with an increased risk of infection.[8]

Factors influencing the quality of bone healing following intralesional curettage and bone grafting are proximal femur location and tumour length. A greater degree of graft filling can contribute to higher bone healing efficiency.[2]

Treatment options for painless benign bone tumours like a simple bone cyst are still up for debate. Currently, treatment of benign bone cysts includes observation, injection of bone marrow or demineralised bone matrix, curettage blended with bone or synthetic grafting, decompression with intramedullary nailing or cannulated screw, or a mixture of these mentioned approaches.[18]

Hirn et al.[6] retrospectively analysed the outcome of 146 benign bone tumours about the knee that had been treated with curettage alone without any augmentation. Following curettage, the mean diameter of the defects was 5.7 (1.3–11) cm. In 88% of the cases, no further intervention after curettage was required and the meantime to full weight-bearing was 6 weeks. They concluded that the most benign defects of bone wouldconsolidate without any adjuvant filling.

The filling of the resulting cavity after GCT treatment affects the patients' curability as well as the structural stability added to the defect. Other benign bone tumour control is unaffected by the type of filling; however, filling of the resulting cavity will remain a point of contention; whether to fill or not to fill will be determined by the extent and size of the lesion, as well as how much structural stability is required for the lesion.The degree of structural stability required determines the need for additional fixation.

Several factors hampered this research. The sample size was limited due to the rarity of these presentations. Also, the difficulty of control as such presentations needs surgical care;the decision is difficult to be determined in advance, to fill or not and to fix or not. The retrospective design with different diagnoses, heterogeneous presentation of the lesions, surgical procedures, curettage method and filling of the resultant cavity may affect the patient outcomes. In future investigations, we will focus on the necessity for filling, further fixation, and consolidation in a specific entity of benign bone tumours.

CONCLUSION

Filling the resulting cavity after removal of the pathological tissues is usually necessary but not always required. This is determined by the type of lesion and the size of the resulting cavity following curettage. Individualised surgery is required; additional fixation should be considered.

ETHICS APPROVAL AND INFORMED CONSENT

The study was conducted after the approval of the institutional review board of Menoufia university-faculty of medicine-EGYPT and written informed consent from patients

COMPETING INTERESTS

No competing interests

FUNDING

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The feasibility of HEAR score in comparison to Modified HEART score as a risk stratification tool for chest pain patients presented to Emergency Department Hospital Universiti Sains Malaysia

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ABSTRACT

Introduction: Risk stratification tools that integrate clinical, ECG findings and cardiac biomarkers have been used to facilitate the management of chest pain patients in the emergency department (ED). We studied the feasibility of history, age, electrocardiogram and risk factors (HEAR) score as a risk stratification tool for chest pain patients presented to ED Hospital Universiti Sains Malaysia (HUSM) in comparison to modified HEART score (MHS) based on major adverse cardiac events (MACE) within 6 weeks' time.

Materials and Methods: We analysed retrospective data of chest pain patients presenting to ED HUSM from 1st June 2020 till 31st January 2021 based on the patient's history, ECG findings, risk factors, age and troponin level. The patients were stratified as low risk (MHS and HEAR score of 0–3), intermediate risk (MHS and HEAR score of 4–6), and high risk (MHS of 7–10 and HEAR score of 7–8). The association of the MHS and HEAR score with MACE at 6 weeks' time was evaluated using simple logistic regression.

Results: This study included 147 patients in the MHS analysis and 71 patients in HEAR score analysis. The incident rate of MACE in low, intermediate and high risk was 0%,16.3%, and 34.7%, in the MHS group, and 0%, 3.22%, and 6.66% in HEAR score group. The mean difference between MACE and non-MACE in MHS and HEAR score groups was −2.29 (CI: −3.13,1.44, p<0.001) and −2.51(CI: −5.23, 0.21, p=0.070), respectively. There was no significant association between the incidence rate of MACE with modified HEART score (MHS) and HEAR score groups (p>0.95).

Conclusion: HEAR score is not feasible to be used as a risk stratification tool for chest pain patients presenting to ED HUSM in comparison to MHS. Further studies are required to validate the results.

KEYWORDS:
Chest pain, risk stratification tool, HEAR score, HEART score

INTRODUCTION

Chest pain is one the commonest symptoms in patients presenting to emergency department (ED), with the incidence rate of 8–19 per 1000 person per year.[1] These patients constitute a logistic and diagnostic challenge to emergency practitioners as to distinguish between cardiac related or nonthreatening disease. Acute coronary syndrome (ACS) must be ruled out in all patients with chest pain. Approximately 2% of chest pain patients with ACS are speciously discharged from the ED, which was associated with a two-fold increase in 30-day morbidity and mortality.[2]

In Malaysia, ACS remained as the leading cause of death comprised of 15% of medically certified deaths in 2019.[3] ACS is a clinical spectrum ranging from unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) to ST segment elevation myocardial infarction (STEMI) depending on the onset and intensity of the coronary artery occlusion.[4] Initiation of treatment for ACS in the emergency setting is based upon clinical evaluation of cardiac ischemia or infarction based on history, electrocardiogram (ECG) changes and elevation of cardiac biomarker.[5]

Risk stratification tools that integrate clinical, ECG findings and biomarkers in chest pain patients have been used to facilitate management of chest pain patients in ED. HEART score, which is an acronyms for history, electrocardiogram (ECG), age, risk factors and troponin level, has the strongest scientific evidence supporting its application and has been validated in many studies performed in theAsia Pacific, United States (US) and Europe.[6] The HEART score was established in the Netherlands in 2008 as a risk stratification tool for patients with chest pain based on their 6 weeks risks of major adverse cardiac events (MACE).[7] MACE is defined as acute myocardial infarction (AMI), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and death due to any cause.[7] The structure of the five classification with a 0, 1, and 2 scoring system aids in stratifying patients with chest pain into scoring system of 0 to 10, which further sub categorised them into low, intermediate, and high-risk groups. Low-risk patients (a score 3 or less) were found to have a low MACE rate (1.7%), are those who are safe for ED discharge without requiring further cardiac evaluation or inpatient admission. On the other hand, higher score was associated with higher incidence rate of MACE (50.5%), warranted additional investigations.[8] In comparison to Global Registry of Acute Coronary Events

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(GRACE) and Thrombolysis in Myocardial Infarction (TIMI) Score, HEART score is superior in discriminating between those with and without MACE in chest pain patients, anddetected the largest group of low-risk patients at the same level of safety.[9]

The original HEART score utilised conventional troponin I as cardiac biomarker. Several studies validated the use of high sensitive cardiac assays which provide excellent sensitivity to diagnose myocardial injury and predicting major adverse cardiovascular events.[10] The performance of a single level of high-sensitivity troponin I (hsTnI), high-sensitivity troponin T (hsTnT)in comparison with conventional troponin I (cTnI) in association with 30-day MACE turned out to be 100% sensitivity.[11] Thus, certain centers have used these highly sensitive troponin assays as cardiac biomarker to diagnose ACS, including Hospital Universiti Sains Malaysia (HUSM). However, this troponin is not available or may be in limited numbers in many medical facilities especially at the district hospitals and primary cares. A modified scoring system without troponin level; HEAR score (History, Electrocardiogram, Age, and Risk factors) is an alternative to help stratifying chest pain patients. This scoring had been validated in a few studies for stratifying chest pain patients in ED and can be used as a guide for early discharge in low risk patients.[12-14]

In this study, we would like to investigate the feasibility of using HEAR score as a risk stratification tool for chest pain patients presented to ED HUSM in comparison to previously practiced modified HEART score which use highly sensitive Troponin T (hsTnT) by looking for the association with 6 weeks' risks of MACE.

MATERIALS AND METHODS

Study design and population

The study was conducted in Emergency Department Hospital Universiti Sains Malaysia (ED HUSM) from June 2020 till January 2021. Hospital Universiti Sains Malaysia (HUSM) is a teaching hospital under the Ministry of Higher Education, recognised as the regional tertiary referral center located in Kubang Kerian, Kelantan.

This study was a retrospective cross-sectional study looking for the effectiveness of HEAR score in comparison to modified HEART score (MHS) as risk stratification tool for chest pain patients presented to ED HUSM. Medical records of patients presented with chest pain in ED HUSM were traced from the records' office. Data for MHS were collected between June 2020 till September 2020, whereas data for HEAR score were obtained between October 2020 till January 2021. It was a shorter period than previous 1-year study plan as data obtained within this 8months' period sufficed the sample size required. Patients of 18 years old or more, having non-traumatic chest pain and had ECG done during the presentation in ED HUSM were enrolled in this study. Patient who developed cardiac arrest, having ST elevation in ECG and those ACS patients without chest pain were excluded from this study. Also, those subgroup of patients with missing data and those who refused any intervention despite being counselled were excluded from this study. Patients' data were extracted and combined in data collection sheet. Sample size for this study was calculated using web calculator, https://wnarifin.github.io/ssc_web.html. The minimum sample size for MHS analysis is 135 and sample size for HEAR score is 63, based on previous study conducted in Japan.13 The Human Research Ethics Committee Universiti Sains Malaysia approved the study (USM/JEPeM/21040340), and informed consent was waived as this was a retrospective non-interventional study.

Calculation of modified HEART score (MHS) and HEAR score

MHS was calculated based on five variables: history, ECG, age, risk factors, and troponin level whereas HEAR Score only used the first four variables of HEART score without troponin level. Patients' history was interpreted based on documentation from the emergency clerking sheet at the initial presentation and was classified as follow: highly suspicious (2 points), moderately suspicious (1 point) and low suspicion (0 point). The 12-leads ECG was reviewed and categorised into three groups: normal or non-specific findings (0 point), complete left bundle branch block or inverted T wave in more than two consecutive leads (1 point) and significant ST-segment depressions in more than two consecutive leads (2 points). In term of age, 0 point was assigned for those below 45 years; 1 point for those of 45 years or between 45 and 65 years and 2 points if age was 65 years or older. As for risk factors of coronary artery disease, the following were considered: hypertension, diabetes mellitus, hyperlipidaemia, positive family history, obesity and current or previous smoking history. In patients without risk factors, 0 point was allocated; one or two risk factors, 1 point was given and in patients with ≥3 risk factors or having previous history of coronary heart disease, 2 points were assigned. To complete the MHS, highly sensitive troponin T (hsTnT) level was measured. If the hsTnT level at admission was below the threshold value for positivity (<0.14 ng/mL), 0 point was given. If the level was high (≥0.14 ng/mL), 2 points were allocated.

According to the total scores, the patients were further classified into lowrisk (MHS and HEAR scores of 0–3), intermediaterisk (MHS and HEAR scores of 4–6), and highrisk (MHS of 7–10 and HEAR score of 7– 8) categories. This classification was based on previous study.[13]

End points

The end points for the study were the occurrence of major cardiac events (MACE) within 6 weeks' time form initial presentation to ED HUSM. MACE is a composite of AMI, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), coronary angiography and death due to any cause.[15] In identifying MACE, we reviewed the paper-based records which included information on clinical records, discharge summaries, revascularisation reports, via direct phone calls to patients or relatives and other relevant data.

Statistical analysis

All data were collected and analysed using IBM SPSS version 26. Continuous data were expressed in term of mean with standard deviation and categorical data were expressed in term of number and percentage. Independent t-test was used

Table I: The baseline characteristics of chest pain patients presented to Emergency Department of Hospital Universiti Sains Malaysia (n=218)

Variable	HEART score n (%)	HEAR score n (%)	Total n (%)
Gender			
Female	47(32.0)	27(38.0)	74(33.9)
Male	100(68.0)	44(62.0)	144(66.1)
Age in years (mean±SD)	58.27(13.36)	57.75(14.23)	58.10(13.62)
MACE			
No	123(83.7)	69(97.2)	192(88.1)
Yes	24(16.3)	2(2.8)	26(11.9)

MACE: major adverse cardiac events
HEAR: history, age, electrocardiogram and risk factors
HEART: history, electrocardiogram (ECG), age, risk factors and troponin level

Table II: The proportion of patients with chest pain presentation to Emergency Department of Hospital Universiti Sains Malaysia based on the risk group and risk stratification score (n=218)

Variable	Risk stratification		Total n (%)
	Modified HEART score n (%)	HEAR score n (%)	
Risk group			
Low	25(17.0)	25(35.2)	50(22.9)
Intermediate	76(51.7)	31(43.7)	107(49.1)
High	46(31.3)	15(21.1)	61(28.0)

Table III: The comparison of mean HEART score between the presence of MACE in patients with chest pain presented to Emergency Department of Hospital Universiti Sains Malaysia based on the risk group and modified score (n=147)

Variable	MACE Mean (SD)	NO MACE Mean (SD)	t-stat (DF)	Mean difference (95% CI)	*p* value[a]
HEART score	7.46(1.50)	5.17(1.98)	-5.36(145)	-2.29 (-3.13, -1.44)	<0.001
HEAR score	7.00(1.41)	4.49(1.91)	-1.84(69)	-2.51(-5.23, 0.21)	0.070

[a]Independent t-test was applied; Normality and equal variance assumptions were met
The Proportion of Patients in Different Risk Groups that Develop MACE within 6 weeks' time Using Modified HEART and HEAR Score

Table IV: The risk stratification score and incidence rate of MACE according to category

Variable	Risk stratification Modified HEART score			HEAR score		
	n (%)	With MACE (n)	Incidence rate of MACE (%)	n (%)	With MACE	Incidence rate of MACE (%)
Risk group						
Low	25(17.0)	0	0	25(35.2)	0	0
Intermediate	76(51.7)	8	10.52	31(43.7)	1	3.22
High	46(31.3)	16	34.78	15(21.1)	1	6.66

Association between the risk group and developing MACE

Table V: The association between high-risk group and developing MACE in chest pain patients presented to Emergency Department of Hospital Universiti Sains Malaysia according to modified HEART score and HEAR score using Simple Logistic Regression (n=147)

Scoring Tool	Variable	B	Odds ratio (95% CI)	Wald statistic	*p* value
Modified HEART Score	Risk group				
	Low	0	1		
	Intermediate	19.06	-	-	>0.95
	High	20.57	-	-	>0.95
HEAR Score	Risk group				
	Low	0	1		
	Intermediate	17.80	-	-	>0.95
	High	18.56	-	-	>0.95

3.6 The Association of Proportion of HEAR Score of ≤4 and >4 With MACE
There was no significant association between HEAR score category and MACE group (p>0.05)(Table VI).

Table VI: Theproportion of chest pain patients developing MACE presented to the Emergency Department of Hospital Universiti Sains Malaysia based on HEAR score category (n=71)

Variable	MACE n (%)	NO MACE n (%)	Total n (%)	*p* value[b]
Score category				0.494
≤4	0(0.0)	34(49.3)	34(47.9)	
>4	2(100.0)	35(50.7)	37(52.1)	

[b]Fisher exact test applied; more than 20% expected count less than 5.

to compare mean difference of the continuous data, whereas simple logistic regression test was used to evaluate the association of the HEAR and HEART score with MACE at 6 weeks' time. Fisher exact test was applied to evaluate significance of association of MACE with proportion of patients having HEAR score ≤4 with score >4. *p* values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 218 patients enrolled in this study encompassed 147 patients (67.4%) in MHS and 71 patients (32.6%) in HEAR score groups. Majority of the patients were male, whereby 100 males (68%) and 47 females (32%) were in MHS group, 44 males (62 %) and 27 females (38%) were in HEAR score group. The mean (SD) age of patients in the MHS and HEAR score group was 58.27 (13.36) years old and 57.75 (14.23) years old, respectively. A total of 24 patients (16.3%) in the MHS group had MACE, and only two patients (2.8%) in HEAR score group had MACE (See Table I).

Proportion of patients according to the risk group and modified score

The proportion of chest pain patients with high risk in the MHS group was 46 patients (31.3%), whereas 76 patients (51.7%) were in intermediate-risk category. In HEAR score group, the total of 15 patients (21.1%) and 31 patients (43.7%) in a high-risk and intermediate-risk group, respectively. Comparing the population of patients, percentage of patients in low-risk category was higher in HEAR score group, 35.2% compared to 17% in MHS group (Table II).

Comparison of risk stratification scores between patients Having MACE and Without MACE

There was a significant mean difference in scores between patients with and without MACE ($p<0.001$) in MHS group. The mean HEART score was found to be slightly higher in MACE and no MACE group in comparison to HEAR score group, with 7.46 and 5.17, respectively. The result indicated no significant mean difference of HEAR score between those with and without MACE ($p>0.05$). (Table III)

The study showed that the highest incidence rate of MACE occurred in high-risk group in MHS and HEAR score analysis with 16 cases (34.78%) and 1 case (6.66%), respectively. No MACE reported in low-risk group for both score (0%) (Table IV).

Based on the MHS and HEAR score, there was no significant association between major adverse effect events and patients in a high-risk group ($p>0.05$). (Table V)

DISCUSSION

Evaluation of clinical symptoms and a prognostic risk stratification should be made in all patients presenting with chest pain, to initiate specific therapy when indicated and reduce avoidable admissions and inappropriate discharges. HEART score has been widely used and validated in counterparts of the world, to aid in the risk stratification of patients with undifferentiated chest pain in the ED.[16] In our local setting in ED HUSM, instead of using conventional troponin, hsTnThad been integrated into modified HEART score, where the cut point of ≥14ng/L is used as positive cardiac biomarker. As we are relying on troponin level to diagnose ACS, restriction, or unavailability of cardiac troponin markers in hospitals may delay management and increase rate of missed diagnosis in ED. In HUSM, due to limited availability of troponin, HEAR score (HEART score without troponin) was applied as the modified risk stratification tool for chest pain patients presented to ED HUSM since October 2020. Numerous validation studies regarding this risk stratification tool for chest pain patients were based on short term major adverse cardiac event (MACE) within 30-days or 6 weeks' time, which include AMI, death , coronary angiogram and CABG.[12-14]

In this study, we found that the majority proportion of chest pain patients were in intermediate risk for both MHS group (51.7%) and HEAR score group (43.7%). Comparing the population of patients, percentage of patients in low-risk category was higher in HEAR score group, 35.2% compared to 17% in MHS group. A total of 24 patients (16.3%) in the MHS group had MACE and only two patients (2.8%) in HEAR score group had MACE. The highest incidence rate of MACE occurred in high-risk group in MHS and HEAR score analysis with 16 cases (34.78%) and 1 case (6.66%), respectively. No MACE was reported in low-risk group for both score (0%). This study also revealed the mean MHS and HEAR score for MACE group was 7.46 (±1.50) and 7.00 (±1.41) in contrast to non-MACE group, mean MHS and HEAR score were 5.17 (±1.98) and 4.49 (±1.91), respectively. The mean difference of MACE and non-MACE group for MHS was −2.29 (CI: −3.13,1.44) which is statistically significant ($p<0.001$), whereas mean difference for HEAR score was -2.51(CI: -5.23, 0.21) which is not statistically significant ($p=0.070$). These results conveyed that those patients with score less than 5 in MHS and less than 4 in HEAR score are less likely to develop MACE.

From our study, we found that there was no significant association between incidence rate of MACE with MHS and HEAR score groups ($p>0.95$). Comparatively, previous study has shown there was a significant association between HEART and HEAR score with MACE, respectively, 100% and

83% sensitive (p<0.001).[13] The proportion of patients in low-risk group for MHS group was 17%, whereas in HEAR score group was 35.1%, which demonstrated 0% occurrence of MACE within 6 weeks' time from first initial presentation. In one meta-analysis encompassing 25 HEART score studies from 2010 till 2017, among patients with low-risk HEART scores, short-term MACE (30 days to 6 weeks) occurred in 2.1% of the population.[17] In comparison, Constable et al and Otsuka et al in their HEAR score studies found that there were 1.7% to 4.7% incidence rate of MACE occurred in low-risk HEAR score group (p<0.001).[12]

In ED HUSM, as per local guideline, patients with HEAR score of ≤4, can be discharged from ED with follow-up, whereas HEAR score of >4 needs to be admitted and investigated further for acute coronary syndrome. From this result, it suggested patients in low risk had very low rate of MACE. Our study reported that the association between HEAR score with MACE was not statistically significant, p=0.494 (p>0.05), with two patients (100%) who had developed MACE were in HEAR score > 4. As shown from the results of this study, low-risk category patient had 0% of MACE, which might suggest for safe early discharge from ED, nevertheless, further validation studies need to be carried out.

A retrospective, double-centred, observational, cohort study in US had found HEAR scores overestimate risk when hs-cTnT<99th percentile, in which they reported that those with baseline quantifiable hs-cTnT within the reference range (<99th percentile), a higher risk (>1%) for 30-day MACE exists even in those with low HEAR scores.[19] In comparison, another study by Smith et alfound that the sensitivity to rule out MACE in very low-risk patients (HEAR score ≤1) wasexcellent with missed rate of 0.9% (95% CI: 0.2%-2.3%).[20] As in our study, we did not perform the troponin testing for patients in HEAR score group, so we could not analyse the sensitivity of HEAR score for low-risk group, thus, further studies need to validate our results.

Apart from emergency department in tertiary hospital, this HEAR score can be used in primary care centres or district hospitals to guide which patients need urgent referral. As those in low risk HEAR score, referral can be as follow ups whereas those in high-risk group need to be referred urgently to tertiary hospital. Additional studies can be done in those centres to look for any significant result. On the other hand, the international guidelines had recommended the use of serial troponin levels as the early risk stratification for chest pain patients.[18,21] HEART pathway, EDACS, ADAPT, 2020 ESC/hs-cTnT pathway are amongst validated studies using serial troponin to identify low risk patients who can be safely discharged from ED which have shown to be effective.[18,21,22] This pathway can be further studied in the Malaysian population to look for diagnostic validity and efficiency.

This current study had limitations. It was a retrospective study design, thus those with missing data including MACE were excluded from the study. We also did not include patient who refused for any intervention like CABG, angiogram, and PCI in this study. We could not explicitly explain how this can affect the trend of the results; thus, it could lead to selection bias. This was a cross-sectional study, with small study population compared to previous studies. A study with larger population involving multicentre should be conducted in the future which will have better representation of Malaysian population that may yield different and/or more significant results. We also did not conduct validity test for this study, looking into sensitivity and predictive values which should be included in the other study.

CONCLUSION

Our study found that there was statistically no significant association of HEAR score in comparison with modified HEART score with MACE (p>0.95). Thus, we would like to conclude that HEAR score is not feasible to be used as risk stratification tool for chest pain patients presented to ED HUSM. A further prospective study can be conducted to validate the results.

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Parental hesitancy and perception of the COVID-19 vaccine for children below 5 years in Cheras district, Kuala Lumpur

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ABSTRACT

Introduction: The use of the COVID-19 vaccine for all children below the age of 5 is expected to be available soon in Malaysia. Hence, this study aimed to assess parental hesitancy and perception of the vaccine.

Materials and Methods: A cross-sectional study was conducted among parents of children below 5 years of age, from July to September 2022 at two urban primary care clinics in the Cheras district of Kuala Lumpur. Hesitance and perception of the COVID-19 vaccine were assessed using a self-administered questionnaire.

Results: A total of 219 completed entries were analysed. The rate of COVID-19 vaccine hesitance for children below the age of 5 was 64.4% (n=141). Univariate analysis showed that vaccine hesitancy was associated with parental age and Muslim religion. The multivariate model showed that younger parents were more likely to be vaccine hesitant compared to older parents. A 1-year increase in parental age showed a 13% decrease in the odds of vaccine hesitancy (AOR 0.87, 95% CI 0.80–0.96). Muslim parents were also more likely to be vaccine hesitant compared to non-Muslim parents (AOR 2.46, 95% CI 1.26–4.79). Most parents perceived correctly that the vaccine can prevent complications and the spread of the disease. However, their main barriers to vaccination were concerns regarding side effects, safety and effectiveness of the vaccine.

Conclusion: Our study found that parents have a high rate of COVID-19 vaccine hesitancy for children younger than 5 years of age. Vaccine hesitancy was associated with parents' age and religion. Most of them perceived that the vaccine could prevent complications and the spread of COVID-19. Their main barriers towards vaccination were regarding vaccine side effects, safety and effectiveness.

KEYWORDS:
COVID-19, perception, vaccine delay, vaccine hesitancy

INTRODUCTION

The coronavirus disease has greatly impacted the health and lives of millions of people around the world. The COVID-19 virus not only affected the adults and elderly but also children and infants. In Malaysia, about 20,000 children under the age of 4 were infected with COVID-19 by October 2022.[1] Most of them were either asymptomatic or presented with symptoms of mild respiratory infection. However, some young children experienced severe infections requiring hospitalisation, intensive care or ventilator support while others succumbed to COVID-19-related death.[2] Following the COVID-19 infection, children are at higher risk of developing cardiovascular, neurological and respiratory complications, as well as a multisystem inflammatory syndrome (MIS-C), especially among unvaccinated children.[3]

In 2019, the World Health Organization (WHO) declared that vaccine hesitancy is one of the global health threats.[4] WHO has defined vaccine hesitancy as "a motivational state of being conflicted about, or opposed to, getting vaccinated; this includes intentions and willingness."[5] The cause for vaccine hesitance is multifactorial. It is found to be related to knowledge, awareness, risk, benefits and fear of vaccination. Socio-demographic and economic factors also have a role.[6] In Malaysia, a study by Panting et al. found that parents' hesitancy to vaccinate their children were associated with a lack of knowledge regarding the adverse effects of vaccines.[7] Other concerns included the *Halal* status of the vaccine and the negative influence of social media which implied that immunisation was a conspiracy. Malaysian parents preferred to use traditional treatments and natural food sources to boost their children's immunity as an alternative to the vaccine.[7]

A study by Ng et al. in Malaysia found that parents of children less than 12 years of age were hesitant to vaccinate their children with the COVID-19 vaccine because they were uncertain about the new vaccine, its contents and its safety. However, they would consider vaccination if it was safe and the outcome as well as the severity of COVID-19 disease among children in other countries was known.[8] Malaysian parents who were younger and misinformed about the vaccine's safety, as well as efficacy, were also less likely to vaccinate their children who are less than 17 years of age.[9] A review article by Hudson et al. showed that vaccine hesitancy among parents in Malaysia was associated with younger parental age and parents with young children. The most common reason for vaccine hesitancy among them was concerning the side effects of the vaccine.[10]

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The Centres for Disease Control and Prevention (CDC) has recommended the COVID-19 vaccination for all children between the ages of 6 months to 5 years, irrespective of their comorbidities or immune status.[11] Currently, there are two vaccines (Pfizer-BioNTech and Moderna) which have been approved by The United State Food and Drug Administration (FDA) for this age group. Recent clinical trials using these vaccines reported mild to moderate side effects and no serious adverse effects following immunisation (AEFI).[12]

In Malaysia, the COVID-19 Immunisation Programme for children between ages 5 to 11 years (PICKids) started in February 2022 with two doses of Comirnaty® (PfizerBioNTech). The Ministry of Health Malaysia (MOH) then extended the use of the COVID-19 vaccine for children between ages 6 months to 5 years starting with those who are immunocompromised or with comorbidities and plan to make it available to all children below 5 years of age.[13] It is unclear if parents would accept the vaccine for their young children as to date, there is no published data on this issue.

The aim of this study is to assess parents' hesitancy and their perception of the COVID-19 vaccine for children below 5 years. It is hoped that the findings from this study would be useful to identify parents' concerns and provide appropriate counselling in the future.

MATERIALS AND METHODS

A cross-sectional study was conducted between July and September 2022 at two urban primary care clinics in the Cheras district of Kuala Lumpur. The two clinics were selected from five clinics that were registered in the district using the fishbowl method. The names of five clinics in this district were written on pieces of paper, folded and kept in a bowl. The researcher then shuffled and picked two at random. The clinics chosen were Klinik Kesihatan Cheras Makmur and Klinik Kesihatan Salak Selatan. Parents from these clinics were approached at the counter upon registration using the convenient sampling method. Those who had children below five years of age and were able to read and write in the local language, Bahasa Melayu were invited to participate in the study. The parents who consented were briefed regarding the study. If both parents were present, either one was given the form to be filled out and collected upon completion. Parents who had more than one child under the age of 5 were asked to answer the questionnaire by keeping in mind their youngest child.

Data were collected using a self-administered form which had three sections. The first section consisted of socio-demographic details of the respondent. The second section assessed parents' acceptance or hesitancy of the COVID-19 vaccine for their children aged less than 5 years. This was assessed using the statement "I would accept the COVID-19 vaccine for my child who is less than 5 years old, once it is available" for which the parent selects one of the five options in the Likert scale (strongly agree, agree, neutral, disagree and strongly disagree). Parents who selected the options "strongly agree" and "agree" were considered to accept the vaccine while those who selected "neutral", "disagree" or "strongly disagree" were considered as vaccine hesitant. Vaccine hesitancy in this study was defined based on the WHO definition as "a motivational state of being conflicted about or opposed to, getting vaccinated: includes intention and willingness."[5]

The third section assessed parents' perception of the COVID-19 vaccine. This questionnaire was developed from a literature search and prepared for local use in Bahasa Malaysia.[14-16] Vaccine perception was assessed using 12 statements in two domains, which were facilitators (4 statements) and barriers (8 statements). For each statement, parents selected one of the three options; "agree", "unsure" or "disagree". Parents who selected "agree" for the facilitator statement were considered to have the correct perception of that statement while those who selected "unsure" or "disagree" were considered to have a misperception of the statement. For the barriers domain, parents who selected the "agree" response for a statement, were identified as barriers while the "unsure" or "disagree" responses were considered as non-barriers. Content validation for this questionnaire was done by an expert panel consisting of two, family medicine specialists and an infectious disease specialist. Face validation was done among ten patients and did not require any changes. A pilot study for internal consistency was done among 30 respondents at a different health clinic and it showed a Cronbach's alpha of 0.70 for the 12-item scale.

To define and classify income groups of parents, the monthly household income was divided into three groups. The low-income group (B40: household income below RM4,850 per month), the middle-income group (M40: household income between RM4,851 to RM10,970 per month) and the high-income group (T20: household income above RM10,971) based on the Department of Statistic Malaysia 2020.[17]

The sample size for this study was calculated using the Kish Formula based on the rate of parental hesitancy towards COVID-19 vaccine by Aedh et al. (72.2%).[18] Using the confidence interval (CI) of 95%, an absolute precision of 6% and an additional 10% for the incomplete response, a sample size was 241 was obtained.

For the analysis, categorical data were described in absolute numbers (n) and percentages (%). Non-parametric variables were presented using median and interquartile range (IQR). Bivariate analysis was done using Chi-square and Fisher-exact tests to establish the relationships between parents' socio-demographic characteristics, their misperceptions and barriers to vaccination. Variables with p values < 0.25, in the bivariate analysis were selected for multivariate logistic regression analysis. Multivariate logistic regression analysis was done using the backwards-step selection method to assess predictors for vaccine hesitancy. The crude and adjusted odds ratio (OR), 95% CI and p-values, were reported for each independent variable. A p-value of <0.05 was considered statistically significant. Hosmer–Lemeshow test and Nagelkerke Pseudo R2 were used to assess the fitness of the model. Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 27. (SPSS Inc., Chicago, IL, USA)

Table I: Demographic characteristics of participants

Demographic characteristics	n (%)
Parent's age	**Median (IQR)**
	32 (6.0)
Relationship with child	
Mother	183 (83.6)
Father	36 (16.4)
Ethnicity	
Malay	166 (75.8)
Chinese	40 (18.3)
Indian	7 (3.2)
Others	
Religion	
Muslim	169 (77.2)
Buddhist	37 (16.9)
Hindu	7 (3.2)
Others	6 (2.7)
Education	
University	122 (55.7)
School	92 (42.0)
No formal education	5 (2.3)
Job description	
Employed	152 (69.4)
Unemployed	67 (30.5)
Household monthly income	
Low	159 (72.6)
Middle	48 (21.9)
High	12 (5.5)

Table II: Parents' hesitancy and perception of COVID-19 vaccine for children below 5 years

Acceptance of future COVID-19 vaccine for children below 5 years		n (%)	
Vaccine hesitancy		141 (64.4)	
Vaccine acceptance		78 (35.6)	
Facilitators	**Agree**	**Unsure**	**Disagree**
The vaccine can prevent complications	116 (52.9)	94 (42.9)	9 (4.1)
The vaccine can prevent spread of COVID-19 infection	110 (50.2)	99 (45.2)	10 (4.6)
The vaccine can protect my children from COVID-19 infection	91(41.6)	113 (51.6)	15 (6.8)
The vaccine is safe for my children	81 (37.0)	123 (56.2)	15 (6.8)
Barriers			
Concern of side effects of the vaccine	152 (69.4)	47 (21.5)	20 (9.1)
Concern regarding the safety of the vaccine	96 (43.8)	90 (41.1)	33 (15.1)
Concern regarding the effectiveness of the vaccine	79 (36.1)	86 (39.3)	54 (24.7)
Fear of needle	75 (33.3)	69 (31.5)	77 (35.2)
The belief that children less than 5 years do not require vaccine	68 (31.1)	101 (46.1)	50 (22.8)
Negative information regarding the vaccine on social media	61 (27.9)	93 (42.5)	65 (29.7)
Vaccination is against my personal belief	30 (13.7)	84 (38.4)	105 (47.9)
Vaccination is against my religion	6 (2.7)	56 (25.6)	157 (71.7)

RESULTS

A total of 241 people fulfilled the inclusion criteria and agreed to participate in this study. However, 22 questionnaires were incomplete. Hence, 219 responses were subjected to analysis. The questionnaire was mostly answered by mothers (83.6%, n=183), from the Malay ethnic group (75.8%, n=166) followed by the Chinese (18.3%, n=40) and the Indian ethnic groups (3.2%, n=7). Most parents were Muslims (77.2%, n=169), had received tertiary education (55.7%, n=122) and were employed (69.4%, n=152). The majority of the parents were from the low-income group (72.6%, n=159) (Table I).

The majority of parents were vaccine-hesitant (64.4%, n=141) while only about one-third of them (35.6%, n=78) were willing to accept the COVID-19 vaccine for their children below 5 years of age.

About half of the parents perceived that the COVID-19 vaccine could prevent complications (52.9%, n=116) and the spread of the virus (50.2%, n= 110). Common barriers to vaccination were concerns regarding side effects (69.4%, n=152), safety issues (43.8%, n=96) and effectiveness of the vaccine 79 (36.1%, n=79). Details of other facilitators and barriers towards the COVID-19 vaccine are given in Table II.

Testing the association between parent's socio-demographic characteristics and vaccine hesitancy showed that age, ethnicity, religion and income of parents were associated with COVID-19 vaccine hesitancy as shown in Table III.

Testing the association between acceptance or hesitance for the vaccine with facilitators and barriers using Chi-square test, showed a few significant associations (Table IV).

Table III: Association between parent's characteristics with vaccine acceptance and hesitancy

Demographic data	Vaccine acceptance n (%)	Vaccine hesitancy n (%)	*p* value
Parental age (years)	Mean (SD)	Mean (SD)	0.02
	33.51 (4.74)	31.87 (5.21)	*T test*
Gender			
Father	12 (33.3)	24 (66.7)	χ^2
Mother	66 (36.1)	117 (63.9)	0.754
Ethnic group			
Malay	50 (30.1)	116 (69.9)	χ^2
Non-Malay	28 (52.8)	25 (47.2)	**0.003**
Religion			
Muslim	51 (30.2)	118 (69.8)	χ^2
Non-Muslim	27 (54.0)	23 (46.0)	**0.002**
Education			
University	45 (36.9)	77 (63.1)	χ^2
School	32 (34.8)	60 (65.2)	0.782*
No formal education	1 (20.0)	4 (80.0)	
Employment			
Employed	56 (36.8)	96 (63.2)	χ^2
Non- employed	22 (32.8)	45 (67.2)	0.568
Income Group			
Low	47 (29.6)	112 (70.4)	χ^2
Middle	23 (47.9)	25 (52.1)	**0.005***
High	8 (66.7)	4 (33.3)	
Child's Comorbidities			
None	68 (34.7)	128 (65.3)	χ^2
Yes (e.g. heart /lung disease/others)	10 (43.5)	13 (56.5)	0.405

*Fisher–Freeman–Hilton exact test, *p* value < 0.05 is significant.

Table IV: Association between perception (facilitators and barriers) vaccine acceptance and hesitancy to COVID-19 vaccine

Facilitators		Acceptance n (%)	Hesitancy n (%)	*p* value
The vaccine is safe for my children	Correct perception	61 (75.3)	20 (24.7)	χ^2
	Misperception	17 (12.3)	121 (87.7)	**<0.001**
The vaccine can protect my children from COVID-19 infection	Correct perception	62 (68.1)	29 (31.9)	χ^2
	Misperception	16 (12.5)	112 (87.5)	**<0.001**
The vaccine can prevent the spreading of COVID-19 infection	Correct perception	70 (63.6)	40 (36.4)	χ^2
	Misperception	8 (7.3)	101 (92.7)	**<0.001**
The vaccine can prevent complications	Correct perception	70 (60.3)	46 (39.7)	χ^2
	Misperception	8 (7.8)	95 (92.2)	**<0.001**
Barriers				
Fear of needle	Non-barrier	49 (62.8)	97 (68.8)	χ^2
	Barrier	29 (37.2)	44 (31.2)	0.369
Concern about side effects of the vaccine	Non-barrier	32 (41.0)	35 (24.8)	χ^2
	Barrier	46 (59.0)	106 (75.2)	**0.013**
Concern regarding the effectiveness of the vaccine	Non-barrier	60 (76.9)	80 (56.7)	χ^2
	Barrier	18 (23.1)	61 (43.3)	**0.003**
Concern regarding the safety of the vaccine	Non-barrier	60 (76.9)	63 (44.7)	χ^2
	Barrier	18 (23.1)	78 (55.3)	**<0.001**
Negative information regarding the vaccine on social media	Non-barrier	60 (76.9)	98 (69.5)	χ^2
	Barrier	18 (23.1)	43 (30.5)	0.241
The belief that children less than 5 years do not require vaccine	Non-barrier	72 (92.3)	79 (56.0)	χ^2
	Barrier	6 (7.7)	62 (44.0)	<0.001
Vaccination is against my personal belief	Non-barrier	72 (92.3)	117 (83.0)	χ^2
	Barrier	6 (7.7)	24 (17.0)	0.06
Vaccination is against my religion	Non-barrier	77 (98.7)	136 (96.5)	χ^2
	Barrier	1 (1.3)	5 (3.5)	0.326

Table V: Multivariate logistic regression for predictors of vaccine hesitancy

Variables		Crude OR[a] (95% CI)	*p*	Adjusted OR[b] (95% CI)	Wald statistics (df)	*p*
Age		0.94 (0.89–0.10)	0.024	0.87 (0.80–0.96)	8.27 (1)	0.004
Ethnicity	Non-Malay	1				
	Malay	2.60 (1.38–4.89)	0.003	1.1 (0.20–11.24)	0.16 (1)	0.68
Religion	Non-Muslim	1		1		
	Muslim	2.71 (1.42–5.18)	0.002	2.46 (1.26–4.79)	6.92 (1)	0.008
Income group	High income	1		1		
	Middle income	2.17 (0.57–8.19)	0.251	1.62 (0.41–6.40)	0.48 (1)	0.48
	Low income	4.77 (1.37–16.59)	0.014	3.56 (0.98–12.93)	3.75 (1)	0.053

For further analysis, independent variables with a *p*-value of less than 0.25 (age, ethnicity, religion, income) were selected for multivariate logistic regression analysis. There was no multicollinearity and interaction between the independent variables tested. The regression model fit reasonably well. After adjusting for covariates, parental age and religion were the main predictors for COVID-19 vaccine hesitancy with significantly high odds. The final model showed that with a 1-year increase in parents' age, there was a 13% decrease in odds for vaccine hesitancy (AOR 0.87, 95% CI 0.80–0.96). Muslims (AOR 2.46, 95% CI 1.26–4.79) had 2.46 times the odds of vaccine hesitancy compared to non-Muslims (Table V).

DISCUSSION

In general, vaccine acceptance reflects the overall perception of disease risk, vaccine attitudes and demand.[19] The rising trend in vaccine hesitancy and delayed acceptance over the past few decades has affected vaccine uptake and resisted efforts in fighting vaccine-preventable diseases.[20] The World Health Organization (WHO) recently declared that vaccine hesitancy is considered a global health threat.[4] Immunisation among children depends on the parents' consent as they are minors. Hence, it is important to study parents' perception, facilitators, and barriers towards the COVID-19 vaccine.

Our study found that the majority of parents (64.4%, n=141), were hesitant to vaccinate their children below 5 years of age with the COVID-19 vaccine and had concerns regarding vaccine safety, side effects and effectives. A high rate of vaccine hesitancy was also found in Saudi Arabia and Thailand, where 56.9% to 72.2% parents of children less than 12 years of age were hesitant and less likely to immunize their children against COVID-19.[18,21] Parents in Thailand were also mainly concerned about the vaccine's side effects (82.5%), safety issues (60%) and efficacy (37.2%).[21] A previous study in New York found that the safety of the vaccine, effectiveness and perceptions that children did not need vaccination, were the primary reasons for vaccine hesitancy.[22] These finding suggests that vaccine safety and efficacy are two very important issues which overwhelmed parents, outweighing the benefits of vaccination. Currently, there are 2 vaccines (Pfizer-BioNTech and Moderna) which have been approved by FDA for this age group. The safety profile of this vaccine was found similar to placebo and it was well-tolerated with mild to moderate side effects.[12] Based on this information, it is important to create awareness among parents regarding the vaccine's safety and side effects profile to enhance its uptake for children below 5 years of age.

Data from our study show that parents' hesitancy to give their children the COVID-19 vaccine was significantly associated with their age and religion. With every one-year increase in parents' age, they had a 13% decrease in odds to refuse the vaccine (AOR 0.87, 95%CI 0.80-0.96) suggesting that older parents are more likely to accept the COVID-19 vaccine. In Malaysia, vaccine hesitancy is generally associated with younger parental age.[10] Another multicentric study from the Eastern Mediterranean Region (EMR) also showed that older parents were more receptive to the COVID-19 vaccine.[23] This EMR study found that parents aged 40 years and above had an OR between 13 to 18 to vaccinate their children below the age of 17 years compared to younger parents. A study from Saudi Arabia also found that older parents were more likely to vaccinate their children because they sought information regarding the COVID-19 vaccine from a reliable source which was the healthcare personnel.[18] The exact cause for vaccine hesitancy among young parents is not clearly known and could be multifactorial. Young parents have less experience vaccinating their children, compared to older ones. Older parents would have experienced safe vaccination for their children in the past and hence may be more receptive towards the COVID-19 vaccine. Providing accurate information regarding the vaccine to young parents may prove beneficial.

Our study showed a significant association between vaccine hesitancy and religion, where Muslim parents had 2.46 times the odds to be vaccine hesitant compared to non-Muslims (AOR 2.46, 95% CI 1.26-4.79). A similar trend was also noted in Bangladesh whereby 45% of the Muslim population refused to vaccinate their children with the COVID-19 vaccine.[24] A previous study done among different communities in Asia, Africa, and South America during the COVID-19 pandemic showed that 84% of Muslims were vaccine hesitant.[25] This could be due to misinformation about vaccination in this community which may have influenced their decision against the vaccine. In February 2021, The National Fatwa Committee of Malaysia announced that the use of the COVID-19 vaccine was permissible.[26] This information needs to be emphasized among Malaysian Muslim parents during counselling to change their perception with the hope to increase vaccine uptake among young children.

Our study did not show any association between low income and vaccine hesitancy. However, a study in Bangladesh found that parents who are from the low social income group and staying in village or semi-urban areas, refused to vaccinate their children.[24] Similarly, a study by AK et al in China also found that regional, cultural, and economic factors have a significant impact on vaccine hesitancy.[16] The exact cause for vaccine hesitancy among the low-income population remains unknown and may be answered by further research using a qualitative design approach. Simas et al, highlighted that the cause may be complex and multifactorial, arising from different cultural backgrounds, ethnicity, religion and socioeconomic factors. Other contributing factors may be social isolation or marginalization by the system and politics.[27] Some of the suggestions to overcome these problems are to train healthcare workers to listen empathetically, address vaccine-related uncertainties and deliver tailored information regarding the benefits of vaccination. This process should ideally be done by working together with the native or religious leaders to alleviate parents' fears regarding the vaccine.[27]

LIMITATIONS

Parents were sampled from an urban setting using the convenient sampling technique, hence the findings may not be a true reflection of the hesitance and perception of the vaccine among the general population. Hence, future studies should include a mixture of sampling of parents from rural and suburban areas. The questionnaires used in this study were not psychometrically validated for Malaysian population. Hence, a proper validation study is recommended in future studies.

CONCLUSION

The majority of parents in our study were hesitant to vaccinate their children below the age of 5 years, with the COVID-19 vaccine. Most parents had correct perception that the vaccine could prevent complications and the spread of the disease; however, their main barriers were concerns regarding side effects, safety and effectiveness of the vaccine. Parents' age and religion were significantly associated with vaccine hesitancy where the younger parents and those from the Muslim religion were more likely to be vaccine hesitant compared to older and non-Muslim parents.

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FUNDING AND CONFLICT OF INTEREST

This study was self-funded, and we declare no conflicts of interest.

ETHICAL APPROVAL

This study was approved by the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee and Institute of Medical Research Ethics Committee (FF-2021-336) and also registered with the National Medical Research Registration (NMRR-21-1901-59694).

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ORIGINAL ARTICLE

Spectrum of cutaneous granulomatous lesions: A 5-year experience in a tertiary care centre in Sarawak

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ABSTRACT

Introduction: Granulomatous skin lesions can have various histopathological features leading to diagnostic confusion. The study aimed to determine the frequency and pattern of different granulomatous skin lesions.

Materials and Methods: This was a 5-year retrospective study done between April 2017 and March 2022 at Dermatology Department, Sarawak General Hospital. Subjects with a clinicopathological diagnosis of granulomatous diseases were included in the analysis.

Results: A total of 1718 skin biopsies were done during the study periods, with 49 (2.8%) confirmed granulomatous skin lesions. Most patients were aged 40–60 with a male predominance of 51%. Most of the skin biopsy samples were taken from the upper limb (36%). In this study, epitheloid granuloma was the commonest subtype (21, 43%) followed by suppurative granuloma (12, 24%), tuberculoid granuloma (8, 16%) and foreign body granuloma (5, 10%). The commonest aetiology of granulomatous skin lesions in our study was infections (30, 61%) followed by foreign body inoculation (8, 16%). Fungal infection was the most common infective cause, followed by cutaneous tuberculosis.

Conclusion: The major cause of granulomatous dermatoses in developing countries is still infections, fungal and tuberculosis being the leading causes.

KEYWORDS:
Cutaneous granulomatous, granuloma, cutaneous tuberculosis, cutaneous fungal infection

INTRODUCTION

Granulomatous inflammation is a chronic inflammatory response with a distinctive tissue reaction pattern. It is characterised by focal clusters of epithelioid histiocytes, multinucleated giant cells, and mononuclear leukocytes. It is a type IV or delayed hypersensitivity reaction induced by infection, reactions to autoimmunity, toxins, allergies, drugs and neoplasms.[1] The cardinal tissue reaction patterns seen in granulomatous skin lesions are predominantly epithelioid granulomas.

Granulomatous dermatoses often present as a diagnostic challenge to dermatologists and dermatopathologists. This is because a single histopathological pattern may be caused by several aetiologies and contrarily, a single aetiology may produce diverse histopathological patterns.[2] Good clinical history, close histological examination and clinicopathological correlation are essential in making a final diagnosis.[3]

The present study was undertaken to determine the frequency and pattern of different granulomatous skin lesions in Sarawak, Malaysia.

MATERIALS AND METHODS

This was a retrospective analysis of all skin biopsy results that were done in the Skin clinic, Sarawak General Hospital in Kuching, Sarawak, Malaysia over a 5-year period from March 2017 to April 2022. All reported cases of granulomatous skin lesions were analysed with regard to clinical information and histopathological examination of biopsy samples. Data analysis was done withthe statistical software SPSS version 23.0.

RESULTS

In this 5 years retrospective study, a total of 1718 skin biopsies were evaluated. Granulomatous skin lesions were diagnosed in 49 cases (2.85%).

Histopathological examination revealed several granulomatous patterns. We observed 21 (43%) epitheloid granulomas, 12 (24%) suppurative granulomas, 8 (16%) tuberculoid granulomas, 5 (10%) foreign body granulomas, 2 (4%) xanthogranulomas and 1(2%) of palisaded granuloma. Amongst these 49 cases, 25 (51%) were males, and 24 (49%) were females (Table I). There was no significant difference in the type of granuloma presentation between males and females (Table III).

The age ranges from 14 to 85 years, with a mean age of 53.5 years. A maximum number of cases occurred in the 40–50 age group followed by the 50–60 age group. Epitheloid granulomas were found in all age groups but doubled up after the age of 30, while suppurative, tuberculoid and foreign-body granulomas were presented at age 40 and above. Age group 20–30 was significantly associated with xanthogranulomas (p=0.008), while the age group 30–40 years was significantly associated with palisaded granulomas (p=0.001), and the age group of more than 70 years was significantly associated with epitheloid granulomas (p=0.044).

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Table I: Distribution of various Histopathological patterns of granuloma according to gender

Type of granulomas	Male	Female	Frequency (%)
Epitheloid	13	8	21 (43)
Suppurative	6	6	12 (24)
Tuberculoid	3	5	8 (16)
Foreign body	3	2	5 (10)
Xanthogranuloma	-	2	2 (4)
Palisaded	-	1	1 (2)
Total	25	24	49

Table II: Site distribution of various granulomatous lesions

Site	Upper limb	Face	Lower limb	Trunk	Neck	Gluteal
Epitheloid	8	7	3	1	1	1
Suppurative	4	2	5	1	-	-
Tuberculoid	5	1	1	1	-	-
Foreign body	1	2	2	-	-	-
Xanthogranuloma	-	2	-	-	-	-
Pallisaded	-	-	1	-	-	-

Table III: Distribution according to the and distribution site

	Total n (%)	Face n (%)	Neck n (%)	Upper limb n (%)	Trunk n (%)	Gluteal n (%)	Lower limb n (%)	*p*-value
Infectious cause								
Fungal infection	12 (40)	0	0	3 (25)	0	0	9 (75)	0.001
Tuberculosis	10 (33)	2 (20)	0	5 (50)	1 (10)	1 (10)	1 (10)	0.254
Atypical tuberculosis	3 (10)	0	0	3 (100)	0	0	0	0.014
Leprosy	4 (13)	1 (25)	0	3 (75)	0	0	0	0.077
Non-infectious								
Foreign body	8 (42)	5 (62)	0	1 (12)	0	0	2 (25)	0.012
Xanthogranuloma	2 (11)	2 (100)	0	0	0	0	0	0.443
Sarcoidosis	2 (11)	0	0	2 (100)	0	0	0	0.048
Granuloma annulare	2 (11)	0	0	1 (50)	1 (50)	0	0	0.100
Others	6 (30)	4 (66)	1 (16)	0	1 (16)	0	0	0.100
Total	49							

Table IV: Distribution according to aetiology and ethnicity

Ethnic	Fungal infection n=12	Tuberculosis n=10	Atypical tuberculosis n=3	Leprosy n=4	Foreign body n=8	Xanthogranuloma n=2	Sarcoidosis n=2	Granuloma Annulare n=2	Others n=6	*p*-value
Malay	2	3	1	1	4	2	0	0	1	0.142
Chinese	4	7	2	2	3	0	0	0	4	0.074
Iban	4	0	0	0	1	0	1	0	1	0.030
Bidayuh	0	0	0	0	0	0	1	1	0	0.080
Melanau	2	0	0	0	0	0	0	0	0	0.011
Pakistan	0	0	0	1	0	0	0	1	0	0.270

Ethnically, Chinese comprised 22 cases (45%), followed by Malay 14 cases (29%), Iban 7 cases (14.2%), and two cases each for Melanau, Bidayuh and foreign nationals (Pakistan). There was no significant association between the type of granuloma presentation and different ethnicities.

The commonest site of granulomas was the upper limb in 18 cases (36%) followed by the face 14 cases (29%) (Table II). Males were significantly associated with a granulomatous lesion on the lower limbs with p=0.025(Table V). There was no significant difference between races in the location of granulomas.

Out of a total of 49 cases, infectious granulomatous dermatoses were seen in 30 (61%) cases and non-infectious in 19 (39%) cases (Table III).

Of 30 infectious granulomatous dermatoses, the most common was fungal granulomatous dermatoses in 12 (40%) cases followed by tuberculosis in 11 (33%) cases. Males and Iban race were significantly associated with fungal granulomatous dermatoses with p=0.025 (Table V) and p=0.030 respectively (Table IV) with a predilection to lower limbs (Table III). Of 12 cases of fungal granulomatous dermatoses, 5 (41%) cases had positive GMS stains. The most common cause of fungal granulomatous dermatoses was chromoblastomycosis 9 (75%), followed by sporotrichosis 2 (16%) and Madura foot 1 (8%). While out of the 10 cases of tuberculosis, only one had positive ZN staining.

Table V:Comparison of granulomatous dermatoses clinical characteristics between male and female patients

Clinical characteristic	Male	Female	*p*-value
Location of lesions			
Face	5	9	0.173
Neck	1	0	0.342
Upper limb	7	11	0.234
Trunk	2	1	0.480
Gluteal	1	0	0.283
Lower limb	9	3	0.025
Types of granulomas			
Epitheloid	13	8	0.336
Suppurative	6	6	0.807
Pallisaded	0	1	0.342
Foreign body	3	2	0.537
Tuberculoids	3	5	0.559
Xanthogranuloma	0	2	0.174
Causes of granuloma			
Infectious	17	13	0.086
Fungal	9	3	0.025
Tuberculosis	4	6	0.622
Atypical tuberculosis	1	2	0.626
Leprosy	2	2	0.898
Non-infectious	6	13	0.086
Foreign body	3	5	0.559
Sarcoidosis	0	2	0.174
Xanthogranulomatous	0	2	0.174
Others (including Granuloma Annulare	4	4	0.850

In the non-infectious category foreign body inclusion reactions, 8 (42%) was the most common, followed by xanthogranuloma 2 (11%), sarcoidosis 2 (11%) and others with one case each was granulomatous type rosacea, ruptured epidermal inclusion cyst, granulomatous cheilitis, mycoses fungoides and pseudolymphoma. One case had an indeterminate cause.

All patients were treated based on diagnosis, with antifungal therapy for cutaneous fungal dermatoses, anti-tuberculosis therapy for cutaneous mycobacterium infection and Bactrim (Trimethoprim/Sulfamethoxazole) for atypical mycobacterium infection. Excision, mainly in non-infectious granulomatous dermatoses, e.g., foreign body granulomas, was performed in 9 cases, resulting in complete resolution of the granulomas. 29 (55.8%) patients recovered, 16 (30.8%) defaulted, 3 had a change of diagnosis and 1 was a non-responder to treatment.

DISCUSSION

Granulomatous skin disease is a distinctive pattern of chronic cutaneous inflammation associated with infectious and non-infectious causes. The distribution of granulomatous dermatoses varies depending on geographic location.[4] Sarawak, which is located in East Malaysia is a highly agricultural state and agriculture and poultry activities dominate the local populace. There is a strong reliance on foreign workers in the palm oil and timber industries.

We observed that epithelioid granulomas were the most common granuloma in our population predominantly in the fifth decade of life with distribution mainly over the upper limbs. Most were infectious in origin. This was in concordance with other studies. In contrast, patients with granulomatous lesions in our population had equal gender distribution. Fungal infection was the most common of the infectious granulomas. These findings were in contrast to previously conducted studies.

Different type of classifications was used by different authors worldwide for granulomatous skin lesions. We have classified granulomatous lesions based on constituent cells and other changes within the granulomas based on George et al., where granulomatous skin lesions are classified as epithelioid, palisaded, suppurative, xanthogranulomatous, foreign body and other granulomatous patterns.[5] They are classified based on characteristic findings found in the histology. Epitheloid granulomas consist of epitheloid histiocytes, or macrophages, a few of which fuse to form cells admixed with lymphocytes and occasional plasma cells with or without features of necrosis.[5] Suppurative granulomas are characterised by epitheloid histiocytes and multinucleated giant cells with a central collection of polymorphonuclear leucocytes and can occur with necrotising or non-necrotising granulomatous inflammation.[6] On the other hand, tuberculoid granulomas are composed of mixed macrophage phenotypes which include epitheloid histiocytes marked by abundant cytoplasmand foamy macrophages with intracellular lipids accumulation. The macrophages can coalesce into multinucleated giant cells, called Langhans' cells.[7] Foreign body granulomas are characterised by the zonal type of granulomatous inflammatory reaction surroundingthe foreign body. Palisading granulomas surround a central focus of degenerated connective tissue, mucin accumulation or fibrin.[8]

Epithelioid type granuloma was similarly the most common type in other studies which were conducted in India, Pakistan and Nepal.[2,3,9-12]

Upper limbs were the commonest site of the lesions followed by the face, similar to a study from Gupta et al.[1] The site of the lesion showed variations in different studies. The most common site of lesion was the trunk followed by the lower limb in India by Kumar, Lalit et al.[13], and in Pakistan, Zafar et al.[11] found the head and neck region to be the most common site followed by lower limb. In our study, atypical mycobacterium infection had predilection in the upper limb, foreign body inclusion in the face and cutaneous fungal infection in the lower limb. This could be job-related such as mycobacterium marinum in a fisherman's hand; however, proper correlation cannot be established due to small numbers.

We observed that granulomatous lesions were common in the 5th decade of life which was similarly reported by Vimal Chander et al.[14] which was a contrast to reports in the third decade in Nepal and India.[3,9,10] There was equal gender distribution in our study, while in other reports from Nepal, Nigeria, Sri Lanka and India there was male gender predominance.[10,15-17] These could be due to geographical differences.

Infectious granulomatous dermatoses (61%) were more common than non-infectious granulomas in our retrospective analysis. Similar results were found by other authors in India.[2,13] Fungal infection was the most common followed by tuberculosis in infectious granulomatous dermatoses. There was no concordance with other reports from India, Nepaland Pakistan. Pawale et al., Adhikari et al., Zafaret al. and Kumar, Lalit et al.[3,10,11,13] found tubercular most common. Gupta et al. from India found leprosy to be more common than tubercular.[2] Pawale et al.[3] found 11.32% fungal lesions in their study while Zafar et al., Bal et al. and Chakrabarti et al. reported 3% granulomatous fungal dermatoses comparatively much lower than our study.[11,18,19] They can manifest as epitheloid and suppurative granulomas. Geographic location probably affected the result as a study conducted in different cities in India yielded different results. Similarly in Sarawak, Malaysia, in the Northern part of Sarawak there is a higher number of cases of leprosy amongst the indigenous Penan people.[20] Thus, if the study was conducted in the Northern part of Sarawak the most common cause of infectious granulomatous dermatoses could be leprosy. Another possibility for the differences could be because cutaneous tuberculosis with concomitant pulmonary tuberculosis may have been treated at a primary care centre leading to lesser referrals to the tertiary centre while all cutaneous fungal infections will generally be referred to Dermatology clinic tertiary hospital for confirmation of diagnosis and management. This could explain the reasons for the high incidence of cutaneous granulomatous fungal infection in our study. Cutaneous fungal granulomatous dermatoses were found in higher proportion in the indigenous Iban male on the lower limbs. Traditionally, the Iban natives are involved in farming. They plant hill paddy, vegetables and fruits and also in oil palm plantations which exposed them to soil. Prolonged work in warm and humid climates, sweating and exposure to infected soil without proper working attire and shoes make them at risk of cutaneous granulomatous fungal infection.

The positivity rate of Grocott-Gomori's methenamine (GMS) staining in cutaneous granulomatous fungal infection is not well described. 5 (41%) fungal granulomatous dermatoses had positive staining with GMS. Two of these had positive cultures with Cladosporium species. Another three patients had negative GMS staining but had fungal bodies seen in histopathology which aided our diagnosis of cutaneous granulomatous fungal infection. The remaining cases were treated with antifungals based on their history and clinical correlation. Amongst them, one patient had no response and required a repeat biopsy and a change of treatment. However, amongst those with either positive staining or fungal body seen in the histopathology, two patients did not respond to antifungal therapy; with one revised diagnosis based on repeat biopsy and another requiring surgical excision. Further study is needed to look into the positive rate of staining and its correlation to fungal cultures. It is a diagnostic and management challenge for cutaneous granulomatous fungal infection.

The incidence of cutaneous tuberculosis in the present study was 0.6%, similar to the worldwide incidence of 0.1-1% of all cutaneous lesions.[3]

Ziehl-Neelsen stain demonstrated acid-fast bacilli only in 10% of our study population. One other study showed a different positivity rate. It can be as low as 5% by Bal et al. whereas it was 11.1% by Adhikari et al., 20.74% in a study by Permiet al., 22.62% in a study by Pawale JS et al., and as high as 71% in a study of Krishnaswamy et al.[3,9,10,18] Cutaneous tuberculosis was diagnosed in the remaining patients based on the presence of positive acid-fast bacilli in tissue culture in two patients and positive tuberculosis polymerase chain reaction (PCR) in one patient and others were empirically treated with anti-tuberculosis medication. Amongst the cutaneous atypical mycobacterium infection, one had positive acid-fast bacilli and one was treated empirically based on history and clinical correlation. Both patients were treated with Bactrim, a sulphonamide antibiotic, with complete resolution. All patients with cutaneous tuberculosis treated with anti-tuberculosis responded favourably.

Detection of tuberculosis, especially in the tissue slides is still based on the histological characteristics of granuloma, which has several differential diagnoses. Ziehl–Neelsen staining has low sensitivity, especially in tissue sections and requires the presence of intact tubercle bacilli.[21] Considering the limitations in sensitivity and specificity of Ziehl–Neelsen staining for mycobacterial detection, mycobacterial culture and molecular and serological techniques, the histomorphological analysis appears to be the only important and feasible technique for the diagnosis of tuberculosis in some patients.[22] However, some tests are not readily available and may have negative results, which leads to the empirical treatment of cutaneous tuberculosis despite the results.

In the present study, foreign body granuloma was the most common type of non-infectious granulomatous dermatoses. This was compatible to Zafar et al.[11] and Pawale et al.[3]

In cases where the staining and cultures were negative, other relevant factors such as occupation and history of exposure to infection may be able to pinpoint the probable aetiology. The morphology of skin lesion might be able to give a clue as well. In the event of a lack of probable aetiology, empirical treatment can be considered, and patients need to be monitored closely on treatment respond. Alternative diagnosis needs to be considered if treatment response is not observed. All the granulomatous skin lesions were correlated with clinical history, examination findings and ancillary investigations before definitive treatment were instituted. 29 (55.8%) patients recovered, 16 (30.8%) defaulted, 3 had a change of diagnosis and 1 was a non-response to treatment. There was difficulty in ascertaining predisposing factors such as comorbid, occupation and history of exposure in developing different cutaneous granulomatous lesions in our population due to incomplete documentation in a retrospective assessment. One-third of patients defaulted to follow-up causing difficulty in ascertaining their treatment outcome. These limitations need to be addressed as they rely on previous documentation on patients' medical records. Therefore, a larger, prospective cohort study in collaboration with the histopathology team is recommended to look specifically into the occupation, socio-economic differences, and comorbidities; different staining, histopathological details and their correlation clinically, which can provide better information, especially on predisposing factors to developing granulomatous lesions. This information would be useful in developing treatment strategies for each granulomatous reaction and in formulating preventive strategies for occupational-related granulomas.

CONCLUSION

Epitheloid granulomas are the most common granuloma pattern in our population. Infectious causes were the major cause of granulomatous dermatoses in developing countries with fungal infection being the most common followed by tuberculosis. The incidence and prevalence of different types of granulomatous dermatoses depend on geographic location. Successful treatment of infectious granulomas would depend on identifying the organism causing each granulomatous reaction and targeted to the infectious disease source. Non-infectious granulomas usually respond well to surgical excision.

ETHICAL APPROVAL

This study was registered via the National Medical Research Register, Ministry of Health Malaysia

CONFLICT OF INTEREST

The authors declare no competing interests

FUNDING

The authors declare no financial disclosure

AUTHOR'S CONTRIBUTION

IPLT was responsible for the study design, data collection and manuscript writing. HZT and HGT participated in data collection and discussion. JWK and MP were involved in manuscript editing and language proofreading. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Rehabilitation characteristics and outcomes of adults with traumatic brain injury: A retrospective study in UMMC, a tertiary centre in Klang Valley

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is a major cause of disabilities among young adults worldwide. Although rehabilitation interventions were shown to reduce the extent of disabilities, there is limited data on the rehabilitation details of TBI patients in Malaysia. This current research is aimed at describing the rehabilitation characteristics of adults with TBI in UMMC, which include the characteristics of patients referred, the rehabilitation setting, intensity of therapy and duration of rehabilitation interventions. Secondly, it is aimed at examining the patients' outcomes at discharge and 1 year.

Materials and Methods: This research is a retrospective review on 201 electronic medical records of TBI patients referred for the multidisciplinary acute rehabilitation. Data on socio-demographic, TBI-related characteristics, rehabilitation details and functional outcomes at admission, discharge and 1-year post-TBI were analysed.

Results: From the study population, males and Malay ethnicity were predominant and the Mean (SD) age was 42 ± 19 years. About two-thirds had severe TBI (63%), with concomitant fractures (70%), and 43% were first referred for rehabilitation during post-traumatic amnesia (PTA) state. 63% of them were directly transferred to the inpatient rehabilitation ward with an average length of stay of 18.8 ± 18.3 days. Only 25% of the patients received the full multidisciplinary team input and interventions during the acute inpatient rehabilitation program. The average hours of therapy received during the acute rehabilitation was 7 hours in a 5 day-week, translating to about 1.5 hours per day. In the first-year post-injury, most patients only received outpatient therapy less than once a month after the rehabilitation discharges. Significant improvements were noted in the Modified Barthel Index, Montreal Cognitive Assessment, 6-Minute Walk Test and Westmead PTA scales from rehabilitation admission to discharge and at 1-year post-TBI (p<0.05).

Conclusion:More than two-thirds of the TBI patients were transferred to the rehabilitation ward within the first three weeks of injury. Significant improvement in general function, cognition, physical mobility and endurance were reported at the rehabilitation discharge and 1 year. These improvements highlight the positive gains of acute rehabilitation interventions after TBI.

KEYWORDS:
brain injuries; rehabilitation; outcome assessment; Malaysia; functional status

INTRODUCTION

Traumatic brain injury (TBI) can be defined as an alteration in brain function or other evidence of brain pathology brought upon by an external force.[1] The global incidence of TBI is on the rise primarily due to an increased use of motor vehicles especially in low- and middle-income countries (LMICs). In some countries, TBI is the leading cause of death with high long-term disability rates.[2,3] This is also true in the Malaysian context, where trauma remains among the top five primary causes of death, especially in the younger age groups.[4] 80% of trauma cases occurred following road traffic accidents with 85% involving the head and neck,[5] leaving TBI an inevitable consequence. The burden of care after TBI in Malaysia includes the loss of productivity and financial independence from an inability to return to work.[6]

Rehabilitation interventions for TBI exist in a large scale which involves a comprehensive multidisciplinary team (MDT). They are typically initiated when patients are deemed medically stable and received definitive treatments. Studies have shown that multidisciplinary inpatient rehabilitation programs and early rehabilitation are beneficial to TBI patients, with improvements seen in terms of cognition, self-care and mobility, shorter duration of coma and length of stay and higher likelihood of discharge to home.[7] However, existing evidence remains limited in LMICs with varying availability of acute rehabilitation resources compared to developed countries.

In Malaysia, referral of patients with TBI to the multidisciplinary rehabilitation team is not part of the standard operating procedure during acute admission. Understanding the referral practice to the rehabilitation team in an acute care hospital, and the characteristics of patients being referred, is crucial to gain further insight into the patients' outcomes. University Malaya Medical Centre (UMMC) is one of the acute centres in Malaysia with a dedicated inpatient and outpatient brain injury rehabilitation program led by the rehabilitation specialists. A previous study at the centre showed that patients with moderate and severe TBI receiving early intensive inpatient rehabilitation have a significantly good outcome at 1 year.[8]

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The TBI patients admitted in UMMC mostly reflect the population in Klang Valley.

Since the referral practices and the rehabilitation details have not been previously explored in the local context, there is a need for further investigation. This research aims to describe the rehabilitation characteristics of adults with TBI at UMMC, including patients referred, the rehabilitation setting, intensity of therapy and duration of rehabilitation interventions. Secondly, it aims to explore patients' outcomes at discharge and 1-year post-injury. This study may provide insights into the effectiveness of the rehabilitation interventions and identify areas for improvement in the management of TBI patients. The findings may also inform the development of evidence-based rehabilitation protocols for TBI patients and contribute to improving the quality of care and outcomes for TBI patients in the local context.

MATERIALS AND METHODS

The present study was approved by the UMMC Medical Research Ethics Committee, with registration number 202162-10191. This is a retrospective study on adults with TBI who received inpatient rehabilitation interventions in UMMC from June 2013 to June 2021. The list of patients was extracted from the departmental referral book and from the electronic medical records. The inclusion criteria were Malaysian adults with TBI, aged 18 and above and referred for rehabilitation interventions to the physician-led MDT. The exclusion criteria were premorbid conditions with other acquired brain injuries, pre-existing cognitive, behavioural and physical disability and history of substance abuse.

The data collected encompasses socio-demographic factors, TBI-related factors, rehabilitation profiles, discharge destination and outcomes assessed during rehabilitation ward admission, at discharge and at 1-year post-TBI. TBI severity was assessed using the initial post-treatment Glasgow Coma Scale (GCS), with scores of 13 to 15 indicating mild TBI, scores of 9 to 12 indicating moderate TBI and scores of 3 to 8 indicating severe TBI.[1] The complete MDT consists of rehabilitation doctors, physiotherapists, occupational therapists, speech and language therapists and rehabilitation nurses, based on the standard practice in UMMC.

Outcome measures included were Modified Barthel Index (MBI), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Berg Balance Scale (BBS), Westmead post-traumatic amnesia (PTA) Scale and 6-Minute Walk Test (6MWT). We selected these outcomes because they were the common outcome measures in rehabilitation practice at UMMC and other rehabilitation practices in Malaysia. We considered an MBI score of >60 to indicate good functional outcomes at discharge from rehabilitation and 1-year post-injury. We screened all records and missing data were classified as unknown.

Statistical Analysis

Analysis of data wasconducted using IBM SPSS Statistic software version 25. Socio-demographic factors, TBI-related factors, rehabilitation characteristics, outcome measures at rehabilitation admission, discharge and 1-year and discharge destination were analysed using descriptive statistics. Continuous variables were reported as median and standard deviations, and categorical variables were reported as numbers and percentages. Non-parametric tests Kruskal–Wallis H and Mann–Whitney U were performed to determine differences in scores of the outcome measures. These tests were also used to determine the association between the demographic factors, injury-related factors and rehabilitation characteristics with good outcomes, defined as MBI >60 at rehabilitation discharge. Statistical significance was taken at p value < 0.05.

RESULTS

A total of 428 names were listed in the referral book but only 201 records were finally obtained from the electronic records and screened because of the difficulties obtaining the full complete older records.

Table I shows the distribution of the patients' socio-demographic and TBI characteristics. Majority of the patients (84.1%) were male, with mean age of 42 ± 19 years old. Half of the patients were married (52.7%). The ethnicity distribution in our patients was similar to the Malaysian ethnicity distribution with majority of them being Malays. For TBI severity, more than half of the patients (63.2%) had severe TBI. Among the severe TBI who were ventilated, the mean duration of ventilation was 9 ± 6.7 days. Only 24% of them were reported to have acute post-traumatic medical complications. Almost two-thirds of the patients (69.2%) had concomitant fractures, and among them, 25.4% were having long bone fractures.

The characteristics of the patients' rehabilitation profiles are shown in Table II. Majority were referred to the MDT by neurosurgeons (88.6%). The remaining patients were referred by a variety of medical professionals including general surgeons, neurologists, orthopaedic surgeons, emergency physicians, general physicians, respiratory physicians, geriatricians, haematologists and fellow rehabilitation physicians from other hospitals. Larger numbers of patients were first referred when they were in the PTA state (43%), followed by patients in the disorder of consciousness (DOC) state (25%). Of those in PTA, 49% were in the stage of acute agitation.

Majority (92.5%) received the first rehabilitation intervention within the first 3 months of injury and at least 63% of the patients received both inpatient and outpatient interventions. 34 patients (16.9%) had multiple admissions to the rehabilitation ward for different rehabilitation interventions and goals throughout the years. Only 24.4% of patients received the complete MDT input and interventions with all team members during the acute inpatient rehabilitation program. Another 69.7% had received inpatient services but not from the complete team of members. The remaining 5.9% received inpatient care exclusively from rehabilitation doctors, due to medical complications developed during the acute rehabilitation care, which prevented them from undergoing active rehabilitation interventions.

Table I: Socio-demographic and traumatic brain injury characteristics of the study population

Variables	N (%)
Age	
18–40	114 (56.7)
> 40	87 (43.3)
Gender	
Male	169 (84.1)
Female	32 (15.9)
Ethnicity	
Chinese	56 (27.9)
Indian	49 (24.4)
Malay	93 (46.3)
others	3 (1.5)
Education level	
Primary	8 (4.0)
Secondary	42 (20.9)
Tertiary	14 (7)
Unknown	137 (68.2)
Marital status	
Single/widowed	91 (45.3)
Married	106 (52.7)
Divorced	4 (2.0)
Place of residence	
Home	193 (96.0)
Hostels	2 (1.0)
Nursing home	5 (2.5)
Presence of medical comorbidities	
No	142 (70.6)
Yes	59 (29.4)
Severity of TBI	
Mild	14 (7.0)
Moderate	60 (29.9)
Severe	127 (63.2)
Aetiology of TBI	
MVA	149 (74.1)
Falls	49 (24.4)
Assault	3 (1.5)
Ventilation	
No	53 (26.4)
Yes	141 (70.1)
Unknown	7 (3.5)
Days of ventilation (mean ± SD)	9 ± 6.7
Post-TBI acute medical complications	
Hydrocephalus	8 (4.0)
Seizure	28 (13.9)
Others	13 (6.5)
Nil	152 (75.6)
Concomitant fracture	
No	62 (30.8)
Yes	139 (69.2)

In the first-year post-injury, most patients received outpatient therapy at a frequency of only less than once a month following discharge from inpatient rehabilitation. Some patients had therapists attended to them in their homes in between hospital therapy schedules, otherwise majority were not able to attend therapy more frequently because of transport and financial issues. Nevertheless, more than one-third of patients had an active follow-up with the rehabilitation team over than 5 years.

Table III depicts the outcome measures at admission, discharge and 1-year post-TBI. There were statistically significant differences in the scores for MBI ($\chi^2(2)=80.617$, $p<0.001$), MoCA ($\chi^2(2)=6.365$, $p=0.041$), 6-MWT ($\chi^2(2) = 24.354$, $p< 0.001$) and Westmead PTA scores ($U=1426.5$, $p<0.001$) from rehabilitation admission. These signified improvement in the overall function, cognition and physical mobility and endurance, respectively. Post-hoc test using the pairwise comparison with a Bonferroni correction for multiple comparisons were performed for groups with $p<0.05$.

The post-hoc test revealed that for MBI, all groups had statistically significant differences ($p<0.001$). For MoCA, there was a statistically significant difference in scores between admission into inpatient rehabilitation and 1-year post-TBI ($p=0.037$), but not at discharge ($p=0.291$). This was also true between discharge and 1-year post-TBI ($p=0.959$). For the 6MWT, all groups had statistically significant differences ($p<0.001$) but not between admission into inpatient rehab and 1-year post-TBI ($p=0.001$).

Table II: Rehabilitation profiles of patients referred to the multidisciplinary team

Variables	n (%)
Referring doctor	
Neurosurgeon	178 (88.9)
Other specialties	17 (8.5)
Unknown	5 (2.5)
Cognitive functioning on the first referral to rehabilitation team according to RLA classification	
1,2,3	51 (25.4)
4,5,6	87 (43.2)
7,8	10 (5.0)
Unknown	53 (26.4)
Interval between TBI onset and first rehabilitation intervention	
24 hours to 21 days post-trauma	152 (76.1)
3 weeks to 3 months post-trauma	33 (16.4)
>3months post-trauma	15 (7.5)
Rehabilitation setting	
Both inpatient and outpatient	132 (65.7)
Inpatient only	67 (33.3)
Outpatient only	2 (1.0)
Types of inpatient rehabilitation services received	
Medical rehabilitation (rehabilitation doctors only)	12 (5.9)
The multidisciplinary team (medical rehabilitation, PT, OT, SLT, rehabilitation nurse)	49 (24.4)
Others	140 (69.7)
Total duration of inpatient rehabilitation stay*	
in days[a] (n=199)	18.8 ± 18.3
Average hours of inpatient therapy per week excluding therapy from rehabilitation nurses (5days/week) [a]	
PT (n=95)	2.8 ± 1.5
OT (n=92)	2.1 ± 1.1
SLT (n=68)	2.0 ± 1.0
Frequency of outpatient therapy in the first year post-TBI	
PT	
Once a fortnight	5 (4.0)
Once a month	28 (22.6)
Less than once a month	91 (73.4)
OT	
Once a fortnight	6 (4.9)
Once a month	31 (25.4)
Less than once month	85 (69.7)
SLT	
Once a fortnight	1 (1.1)
Once a month	10 (10.9)
Less than once a month	80 (87.9)
Frequency of rehabilitation medicine specialist clinic follow-up after discharge	
3 monthly	20 (10.0)
6 monthly	20 (10.0)
6–12 monthly	161 (80.1)
Duration of active follow-up with rehabilitation medicine specialist	
1–2 years	4 (13.8)
>2–5 years	14 (48.3)
> 5 years	11 (37.9)
Total duration of active rehabilitation	
<1 month	58 (28.9)
1–12 months	61 (30.3)
>12 months	82 (40.8)
Discharge destination*	
Home	181 (90.0)
Institutions and other hospitals	16 (8.0)
Mortality	4 (2.0)

* During the first rehabilitation admission [a] Mean ± SD
RLA = Ranchos Los Amigos, PT = physiotherapy, OT = occupational therapy, SLT = speech and language therapy

Table III: Outcome measures during rehabilitation admission, discharge and 1-year post-discharge

Variables	Sample size (n)	Mean ± SD	Mean Rank	*p*
MBI score [a]				< 0.001*
Rehab admission	111	22.2 ± 23.9	91.27	
Rehab discharge	142	52.5 ± 23.3	156.73	
1-year post-TBI	20	90.1 ± 20.7	240.08	
MMSE score [a]				0.129
Rehab admission	20	22.7±6.1	39.03	
Rehab discharge	50	24.7±4.9	50.26	
1-year post-TBI	28	24.6 ± 6.7	55.63	
MoCA score [a]				0.041*
Rehab admission	5	18.6 ± 4.7	8.80	
Rehab discharge	12	23.0 ± 5.9	18.58	
1-year post-TBI	22	25.3 ± 3.9	22.57	
BBS score [a]				0.071
Rehab admission	15	42.8 ± 17.4	23.97	
Rehab discharge	39	42.5 ± 11.7	34.44	
1-year post-TBI	11	46.1 ± 12.7	40.23	
Westmead PTA score [b]				< 0.001*
Rehab admission	66	4.4 ± 3.7	55.11	
Rehab discharge	75	8.6 ± 3.0	84.98	
6MWT score [a]				< 0.001*
Rehab admission	6	157.8 ± 85.1	65.19	
Rehab discharge	28	176.3 ± 113.9	98.13	
1-year post-TBI	10	213.4 ± 104.8	72.18	

[a] Kruskal–Wallis H test.
[b] Mann–Whitney U test.
* Significant difference (<0.05)
MMSE = Mini mental state examination, MoCA = Montreal cognitive assessment, BBS = Berg balance scale, PTA = Post-traumatic amnesia, 6MWT = 6 minute walk test

DISCUSSION

This is the first study describing rehabilitation characteristics of adult TBI patients receiving the multidisciplinary physician-led rehabilitation interventions in a local setting. It was found that patients with TBI were mainly referred by neurosurgeons since UMMC is a tertiary medical centre with the availability of in-house neurosurgeons. However, it is interesting to note that at least 11% of the patients were also referred by other specialties, presuming the patients were admitted in their wards due to other medical complications apart from the TBI. This reflects the awareness of rehabilitation referral for TBI patients among other medical professionals too.

The interval between TBI onset and rehabilitation admission in UMMC was also shorter, which was at three weeks, compared to other neighbouring countries. In contrast, a multicentre study performed at 14 tertiary care centres with inpatient rehabilitation services across Thailand reported that the average duration between injury onset and rehabilitation admission was 5 months.[9] Previous studies have shown that early inpatient rehabilitation by the MDT within 35 days, leads to greater and sustained functional improvements.[9] Benefits include earlier gains in independence, improved mobility, reduction in coma length and length of stay, higher cognitive levels at discharge and home discharge.[7,10-12] This practice also complies with the clinical practice guideline for rehabilitation of adults with TBI which recommended that timely specialised interdisciplinary rehabilitation services must be initiated soonest after achieving medical stability.[13]

Almost half of the patients were referred while in PTA. This is a specific stage of TBI recovery with key features of anterograde memory impairment, confusion and agitation. At this stage, rehabilitation intervention focuses on the integrated reality orientation program while managing the agitation and confusion. A more intensive rehabilitation therapy is introduced gradually.[13]

The availability of resources in the UMMC rehabilitation ward to handle acute agitation in TBI patients has allowed the early transfer of patients in this stage from the acute ward to initiate rehabilitation. These facilities include padded rooms, Posey bed and rooms with reduced stimulation.

Patients in DOC (coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state) were the second commonest types of patients referred for inpatient rehabilitation in UMMC. The rehabilitation interventions for these patients included comprehensive early detection of covert motor and cognitive function, promotion of recovery via neuromodulation techniques, management of generalised spasticity and supportive care. Emerging evidence suggests that covert consciousness is present in up to 15–20% of patients with DOC and that early detection can predict functional recovery at 1-year post-injury.[14] This knowledge can benefit the rehabilitation team to mobilise resources optimally.

The recommended hours of therapy per day in medically stable TBI patients admitted to rehabilitation centres should be at a minimum of 3 hours per day.[13] However, this study

showed that average hours of therapy received during the acute rehabilitation admission was about 7 hours in a 5 day-week, which translated to about 1.5 hours per day. We want to highlight that this therapy duration excluded the therapy provided by the rehabilitation nurses in the ward. There was a difficulty to differentiate between the active therapy provided by the rehabilitation nurse and the acute nursing care from the electronic medical records available. The role of rehabilitation nurses is relevant in all phases of rehabilitation care. In the post-acute stage, they play an essential role in ensuring mobility and self-care including educating the patient and caregivers. Apart from supporting specific interventions such and bladder and bowel management, they also play a part by providing the cognitive behavioural treatments during PTA and agitation.[15] This is considered a type of therapy session.

The other possible reasons for a lower intensity of therapy in UMMC include the fact that TBI patients in UMMC were transferred much earlier from the acute surgical wards when they were still having excess lethargy and sleep disorders such as hypersomnolence, at higher risk of developing acute medical and surgical complications which required transfer to the acute surgical ward for procedures, and the caregiver was not able to fully participate with therapists for the DOC program. All these halted the therapy sessions temporarily. Limitation of manpower was also another reason for the average lower intensity of therapy compared to other studies conducted in developed countries.

We found that there were significant improvements in all outcome measures from admission to discharge and 1-year post-TBI, except for BBS and MMSE. BBS usually detects higher balance capabilities which normally takes more than 1 year to achieve in severe TBI. As for MMSE, it is not sensitive to detect further cognitive improvement as compared to MoCA. Therefore, when we examined the cognitive function using MoCA, there was a significant improvement from admission to discharge. These improvements highlight the positive gains of acute rehabilitation interventions despite the suboptimal intensity of rehabilitation compared to other centres in developed countries.[11]

The finding from our study showed that the average frequency of outpatient rehabilitation therapy within the first year of TBI was less than once a month after discharged from the rehabilitation care. Rehabilitation programs are highly individualised to each patient and therefore the outpatient follow-ups among patients in UMMC were also highly variable. For example, some patients received weekly outpatient therapy for the first few months' post-injury however towards the end of the first year, therapy sessions were more spread out. The high cost of travelling and attending the therapy sessions in UMMC[16] may have contributed to the hesitancy of patients and family members to come more frequently.

Notwithstanding, we also found that more than 85% patients still have an active follow-up duration of more than 2 years. To date, there has been no consensus on how frequent follow-ups should be conducted. Barnes MP[12] has shown that routine follow-ups significantly reduce social morbidity and severity of symptoms via the offering of additional information, advise, support and further interventions. They have recommended that long-term support is maintained for some time after discharge, for at least 2 years, which complies with the standard of practice in this study. Due to the regular follow-up of longer than 2 years in UMMC, long-term recovery patterns and complications that can impede optimal recovery were detected early. In our study, 16.9% of the patients were offered re-admission for intensive rehabilitation to address different goals and objective, based on the condition reviewed in clinic.

The heterogeneity of the rehabilitation interventions and the types of patients admitted (in DOC, in acute agitation, in amnesia state) caused difficulty to examine the association between the different rehabilitation intensity and frequency; with the overall outcome at rehabilitation discharged. The retrospective nature of this study is also another limitation with a lot of missing details of the specific interventions provided. Despite these limitations, we believe that our findings can improve the understanding of local rehabilitation characteristicsof TBI patients and assist in the plan to improve the process of referral for rehabilitation. Future studies can be conducted using a prospective, multicentre cohort study and to use standard rehabilitation interventions suggested.

CONCLUSION

The characteristics of adult TBI patients receiving acute inpatient rehabilitation interventions in UMMC were similar to that reported globally. Majority of the patients were referred during the post-traumatic amnesia state within the first 3weeks of injury, and rehabilitation interventions were promptly initiated. Improvements in functional, physical and cognitive outcomes were significantly noticed at discharge after an average of 3weeks duration of inpatient rehabilitation care. These improvements highlight the positive gains of acute rehabilitation interventions after TBI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Thyroid function status evaluation in patient post-radiotherapy for nasopharyngeal carcinoma: A retrospective study

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ABSTRACT

Introduction: Nasopharyngeal carcinoma (NPC) is among the most common malignancy in Malaysia. Radiation-induced hypothyroidism has been reported in other countries. However, in Malaysia, no studies were ever done to determine the effect of radiation on hypothyroidism. The objective of this study is to evaluate the practice of taking thyroid function test (TFT) and determine hypothyroidism post-radiation in patients with NPC.

Materials and Methods: A retrospective study on the symptoms and results of TFT according to the dosage of intensity-modulated radiotherapy (IMRT) given to patients with NPC. Data were traced and analysed.

Results: A total of 78 patients were identified. All patients received IMRT with 33–35 fractions of radiotherapy (RT) with total dosage of 66–70 Gray given. Not all patients had their thyroid function status measured routinely. Twelve patients did have symptoms of hypothyroidism. TFT were obtained in this group but the results were normal. No correlation was found between RT and hypothyroidism.

Conclusion: There was no correlation between IMRT and the development of hypothyroidism. A prospective study with better control of inclusion and exclusion criteria, and longer follow-up period with TFT, is needed to demonstrate the consistency of these findings.

KEYWORDS:
Hypothyroidism; nasopharyngeal carcinoma; radiation-induced

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the fourth most common malignancy in Malaysia.[1] It is common among the Chinese, followed by natives of Borneo (especially Bidayuh) and Malay.[1] Depending on the year after completion of treatment, follow-up varies from every month to every year.[1] The mainstay treatment of NPC is radiotherapy (RT), or in combination with chemotherapy. Recent management of NPC usually involved the addition of chemotherapy to RT. A meta-analysis conducted in 2015 confirmed that the addition of chemotherapy to RT significantly improves survival in patients with loco-regionally advanced NPC.[2]

Conventional RT involved the delivery of a complete radiation dose over several occasions. It uses high-energy X-rays to shrink or destroy tumour cells. The gap in between radiation allowed for normal cells to heal. Intensity-modulated radiotherapy (IMRT) uses a linear accelerator to precisely deliver a higher radiation dose conform to the shape of the tumour. By doing so, it reduces the damage to surrounding tissues. Study published in 2016 showed IMRT usage is gaining popularity with only 1.5% usage in 2000 but increased to 48.6% in 2007 while the usage of conventional RT decreased from 98.5% to 51.4 %.[3] No study after 2016 was found on literature search. There were no studies in Malaysia showing the percentage of IMRT and conventional RT in use currently.

Radiation-induced hypothyroidism is not uncommon.[4,5] The incidence of hypothyroidism in NPC patients is increasing trend based on duration post-RT.[4,5] The level of thyroid hormone is in a decreasing trend post-RT for 0 to 30 months and reaches a steady state by 36 months.[2] Damage to the hypothalamus-pituitary-thyroid axis may result in hypothyroidism.[6] Thyroxine is usually started as treatment if hypothyroidism is detected.[6] The incidence of radiation-induced hypothyroidism of head and neck cancer is 6–20% while the incidence of subclinical hypothyroidism is 24–50%.[7] Up to 23.2% of patients developed radiation-induced hypothyroidism in NPC.[5] Evaluation of thyroid function is recommended at 1,2 and 5 years.[8]

IMRT showed a reduction in radiation xerostomia in early-stage disease.[8] It poses possibility that it will also reduce the hypothyroidism complication. Radiation-induced hypothyroidism is significantly related to the patient's age, radiation dose, gender and clinical stage.[9] The usage of neoadjuvant RT with IMRT and concurrent chemoradiotherapy with adjuvant chemotherapy showed that both results were similar.[10]

This study aims to determine the level of thyroid function post-RT in NPC patients. Our specific objectives were first to identify the number of patients' thyroid function test (TFT) taken among study subjects and the time it was taken. Secondly to determine the association between underlying illness, gender, stage at diagnosis, type and dose of RT and the proportion of causation of radiation-induced hypothyroidism.

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Table I: Percentage of patients according to fraction of RT

	Frequency	Percentage
Tx32	3	3.8
Tx33	28	35.9
Tx35	47	60.3
Total	78	100.0

Table II: Number of patients with symptoms and percentage of TFT taken

Variables		n	(%)
Symptomatic hypothyroidism	No	66	84.6
	Yes	12	15.4
Sample TFT taken	No	66	84.6
	Yes	12	15.4

Table III: Correlation between comorbidities, fraction of RT and hypothyroidism

Variables		Crude Odd Ratio (OR)	95% (Lower,	CI Upper)	*p* value*
Age		1.020	.974	1.069	.396
DM	No	1			
	Yes	1.409	.144	13.820	.768
HPT	No	1			
	Yes	.625	.124	3.156	.569
HLP	No	1			
	Yes	.509	.059	4.392	.539
IHD	No	1			
	Yes	1.409	.144	13.820	.768
Comorbidities	No	1			
	Yes	.900	.174	4.649	.900
Tumor	1	1			
	2	.279	.028	2.751	.274
	3	.679	.109	4.240	.678
	4	1.484	.340	6.478	.599
Nodular	0&1	1			
	2&3	3.000	.737	12.219	.125
Metastasis	0	1			
	1&x	.284	.034	2.374	.245
Treatment	Tx32+33	1			
	Tx35	.910	.261	3.174	.882

MATERIALS AND METHODS

Study Design

This was a retrospective study approved by Human Research Ethics Committee USM (JEPeM Code: USM/JEPeM/21030244) on 22nd August 2021. National Medical Research Register (Research ID: 58392) was obtained on 30th April 2021.

The sample was obtained from a list of patients under the follow-up of Otorhinolaryngology clinic in Penang General Hospital (PGH), as defined in the inclusion and exclusion criteria. The inclusion criteria included all NPC patients who had completed RT. This study excluded patients with recurrence and those who had previous thyroid surgery. A convenient sampling method was used for the selection. Planning of oncological treatment was done by the radiation oncologist as per standard practice.

Subjects

All patients diagnosed with NPC from the year 2016 to 2020 who came for follow-up in PGH. Data obtained from cancer registry and records of patients were traced. A total of 113 patients were diagnosed with NPC and came for follow-up in PGH. From an expected prevalence of 20%, the calculated sample size was 78, from a finite population of 113.[6]

Sample Collection

All data were collected using the study proforma which included the patient's age, gender, race, comorbidities, number of fractions of RT received, whether a TFT was taken, and the results if the TFT taken.

Statistical Analysis

Categorical data were presented as frequency and percentage while numerical data were presented as mean and standard deviation (SD). We applied simple logistic regression tests in the univariate analysis. Variables comparison with a P-value less than 0.05 is considered as significant. The data were analysed using SPSS software version 26.

RESULTS

The data showed that up to 86% of cases were from Chinese (Figure 1). The majority of cases came from the age group 41–60 (Figure 2).

From the 78 samples collected, the mean age of patients at diagnosis was 53.68 years old. About 60.3% of patients (n=47) received 35 fractions of RT, meanwhile 35.9% of patients (n=28) received 34 fractions of RT and 3.8% of

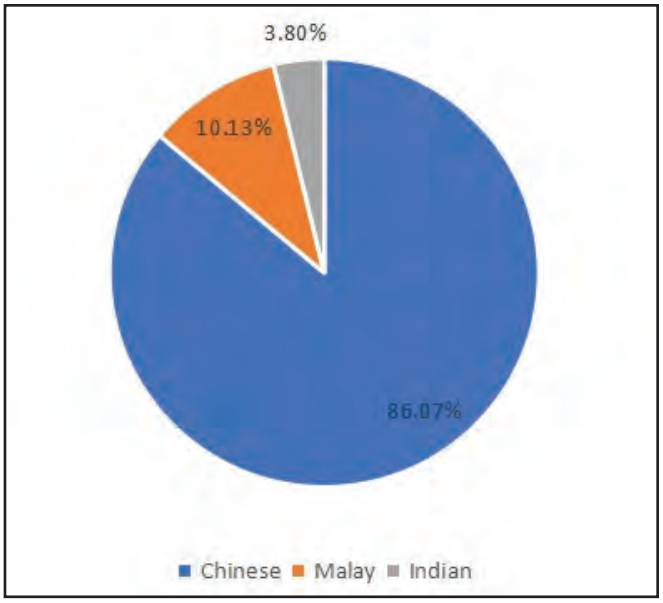

Fig. 1: Percentage of cases of NPC according to race

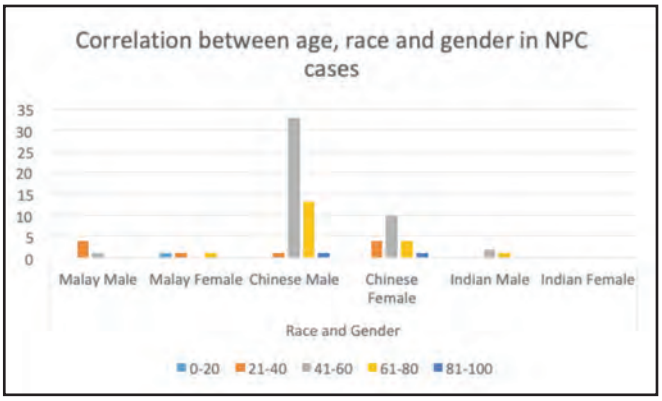

Fig. 2: Number of cases of NPC according to age group with race and gender comparison

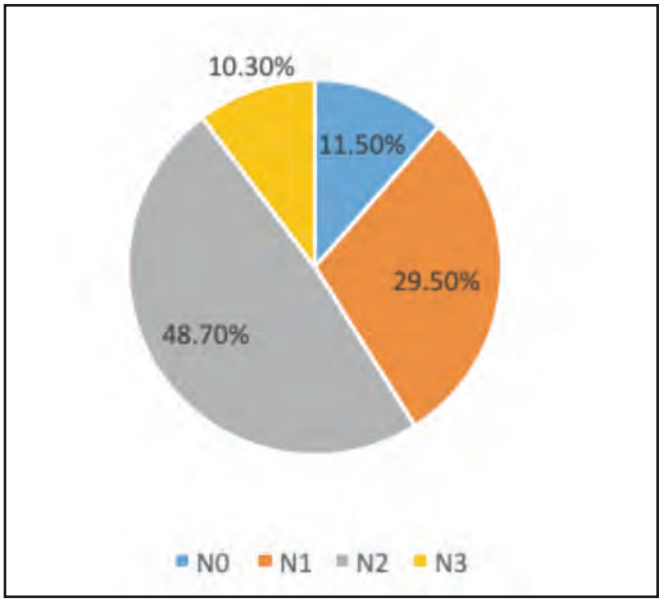

Fig. 3: Neck nodes presentation

patients (n=3) received 33 fractions of RT (Table I). All patients have concurrent chemotherapy and RT.

Tumours were staged according to TNM classification. Nine patients (11.5%) presented with no neck nodes, 23 patients (29.5%) had N1 nodes, 38 patients (48.7%) had N2 nodes while 8 patients (10.3%) had N4 nodes (Figure 3).

Twelve patients (15.4%) reported with symptoms of hypothyroidism during follow-up and their TFTs were taken. In all 12 patients, the TFT results were normal; hence, none of them was started on thyroxine. No follow-up TFT was taken for all 12 patients as results were normal and patients did not complain of further symptoms. Other 66 patients (84.6%) did not complain of symptoms of hypothyroidism, and no TFT was taken (Table II).

There is no correlation between comorbidities and hypothyroidism (p=0.9). For RT and correlation with the development of hypothyroidism, results were not significant as well (p=0.882). The number of fractions on RT given did not affect the development of hypothyroidism as p>0.05 no matter 33, 34 or 35 fractions of RT given (Table III).

DISCUSSION

It was expected up to 23% of patients develop hypothyroidism post-RT in NPC.[5] From our study, it did not show any findings of hypothyroidism as expected biochemically.

The results showed that even though up to 15.4% patients report symptoms of hypothyroidism but blood investigation revealed normal results. Patients were reported to have comorbidities like diabetes mellitus, hypertension, hyperlipidaemia and ischaemic heart disease. However, comorbidities did not have any significance on the report of symptoms of hypothyroidism. A literature search on correlation between comorbidities and hypothyroidism in NPC did not produce any findings.

Amongst our reviewed patients, the hypothyroid symptoms were subjectively reported. Later it was objectively quantified by the normal TFT in all 12 patients. As the patients have no more symptom after the normal TFT was obtained, no further blood takings or any additional investigations were carried out.

According to the Clinical Practice Guideline (CPG) on NPC published by the Ministry of Health Malaysia in 2016, thyroid function was supposed to be taken on each patient on a yearly basis.[1] This study revealed that blood was not taken in every patient but was selectively taken only in those who report symptoms of hypothyroidism. Despite only taking blood in symptomatic patients (which are more likely to have hypothyroidism), the results were normal. Thus, a revision of

CPG may be needed as taking TFT in all patients post-RT may not be suitable as prevailed in this study that even those with symptoms may have normal results. Further larger-scale studies may also be warranted to determine the need for yearly blood investigations. Asymptomatic patients may not consent to an additional blood taking as it requires an extra trip to the hospital. Another clinical audit is needed to determine the factors why blood investigations were not done in the clinical setting.

As for RT, the fraction of RT given was interpreted and showed that it did not cause the development of hypothyroidism. RT given was between 32 and 35 fractions and it depends on the stage of tumour diagnosed and the dose given on each session. As all patients in our studies were given IMRT, and it is known that the effect of IMRT which has been reported to produce lesser toxicities.[11] IMRT was also reported to produce lesser hypothyroidism compared to conventional RT.[11]

It is easy to understand that IMRT delivers full 70Gy for the gross tumour volume, GTV (actual gross tumour showed on CT/MRI) including the lymph nodes (LN) involved. A margin of 5mm from GTV, known as clinical target volume (CTV) will receive the same dose. Other CTV includes the drainage LN, will receive 60-63Gy. If GTV is a central organ, bilateral LN from level II to V will receive 60-63Gy. Other structures for example thyroid gland, pituitary or hypothalamus, are not included in the contouring. However, the radiation effect can be expected depending on how close it is to the targeted organ.

The incidence of subclinical hypothyroidism was between 24 and 50%.[7] As patients with subclinical hypothyroidism may not show symptoms, it was not known the percentage of patients that presented with subclinical hypothyroidism. However, from the results obtained, some patients presented with symptoms but the results were not hypothyroid, it can be concluded that those with subclinical hypothyroidism did not proceed to become hypothyroidism or have yet to develop hypothyroidism. About 2–5% of patients with subclinical hypothyroidism developed overt hypothyroidism.[12] No patients were started on thyroxine replacement in our study, as the TFT results taken were normal or patients were asymptomatic without blood investigation. It was assumed that those asymptomatic have normal thyroxine levels.

A study done by Wu et al. showed that the risk of clinical hypothyroidism increases after 10 years of follow-up. The incidence was up to 19.1% from the study published in 2010.[7,13] In our study, the retrospective data were collected only for patients that had NPC for the last 5 years. Thus, there was a possibility that in longer follow-up, few may present with hypothyroidism. There were no differences in blood investigation among patients who had undergone IMRT and conventional RT according to the CPG.[1] Blood investigation, according to the type of RT given, may be more practical.

If annual TFT was taken as per CPG, it is believed that patients with subclinical hypothyroidism may be detected. However, based on the results, no patients had subclinical hypothyroidism as they may have recovered without being detected. The risk of developing hypothyroidism in patients who received IMRT was lower to begin with as well.[11] Those with subclinical hypothyroidism but with a TSH less than 10mIU/L may not need treatment.[12] This has raised the further question that if an annual TFT is needed. If patients develop subclinical hypothyroidism and recover without being detected, the blood taking may just add to increase cost, resources to the hospital, and to some extent, anxiety unnecessarily.

One of the reasons why no case of hypothyroidism was detected in our study can be due to the age at diagnosis. In our study, the mean age at diagnosis was 53 years. The risk of developing hypothyroidism post-RT increase in the younger age group.[13,14] However, both studies observed the effect of hypothyroidism post-conventional RT; therefore, their study findings may not be accurately compared with our study.

CONCLUSION

Bearing in mind that radiation-induced hypothyroidism is a late toxicity that may take many years to develop, long-term follow-up is needed. If this finding is consistent with a prospective review of TFT post-RT amongst the NPC patients, the yearly thyroid function monitoring may not be needed and can only be taken depending on the type of RT received by patients. A prospective study with better control of inclusion and exclusion criteria, and longer follow-up period with TFT, is needed to demonstrate the consistency of these findings.

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ORIGINAL ARTICLE

A comparative study of microwave oven-assisted tissue processing and conventional method of tissue processing on turnaround laboratory time and morphological quality of tissue sections

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ABSTRACT

Introduction: The purpose of tissue processing is to fix the tissue in a solid medium toenable thin sections. Conventional method of tissue processing is the standardized method of tissue processing which has been used for more than 10 decades. However, the conventional method is time-consuming, and the overall turnaround time for the histopathology report is at least two days. The objective of this study is to identify the protocol for tissue processing procedure using domestic microwave oven. To determine the tissue processing time when using domestic microwave oven. To compare the morphological quality of tissue slides made by domestic microwave oven and conventional method using automated tissue processor.

Matrials and Methods: The conventional protocol and three microwave protocols of tissue processing were used in this study. A pilot study was done prior to the real run to determine the baseline timing for microwave protocol. The baseline timing was fixed at 2 minutes,30 minutes,5 minutes and 25 minutes. The processing time of the microwave protocol was adjusted from 62 minutes to 70 minutes to 77 minutes by increasing the dehydration and wax impregnation time while the time for tissue fixation and clearing remain the same throughout all the microwave protocols.

Results: The group 2 microwave protocol produced the sections that is closely comparable to group 1 conventional protocol. The morphological quality of histopathology slides is best observed when the processing time of microwave protocol is 62 minutes.

Conclusion: The most appropriate microwave protocol for tissue processing is group 2 as the morphological quality of histopathology slides are more superior than that of group 1 with an overall percentage of 80% of satisfactory slides in group 2 and 76.68% in group 1.

KEYWORDS:
Tissue processing, microwave, histopathology, morphological quality

INTRODUCTION

A histopathology slide that is viewed under microscope by pathologist is produced through tissue processing in the histology laboratory for diagnosis.[1] Tissue processing is a procedure that needs to take place between tissue fixation and the sectioning or embedding of paraffin blocks and it comprises of four steps which are dehydration, clearing and impregnation. Tissue processing is very important because when the tissue samples are not properly processed, there might be difficulty in sectioning the tissue samples, and therefore the microscopic information produced will not be helpful.[2]

It is undeniable that tissue biopsy and diagnosis areindeed important for appropriate patient management and choice of therapy. To get the tissue diagnosis from histopathologist, the tissue must first be processed. In routine histopathology laboratory, the tissue samples are processed by automated tissue processor. This conventional procedure has been standardised and used for more than ten decades. Thus, conventional tissue fixation and processing remain as the gold standard against all new technologies and methods.[3] However, routine processing requires many steps and take time, which can delay the diagnosis and management of the patient and lead to serious consequences. It takes approximately 12 hours for tissue to be processed in automated tissue processor machine, and therefore the overall turnaroundtime for the report of tissue biopsy by a histopathology laboratory is at least 2 days.

Microwave ovens arenow used widely in laboratory. For example, microwave oven is used in the laboratory for drying glassware, regeneration of drying material and activation of thin-layer chromatography plates. Besides that, microwave ovens have also become increasingly popular for use in tissue processing and is found to be useful for tissue processing in a short time.[4]

MATERIALS AND METHODS

This study was done at the research laboratory, International Medical University, Malaysia during the period of April 2018 – September 2018. The study samples included soft tissues and visceral organs which were randomly selected from the

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university's animal house. Hard tissue samples such as bone tissues were excluded from the study.

Tissue Processing with Conventional Tissue Processor
Tissue samples were placed in plastic cassettes and processed using Leica automatic tissue processor on an overnight programme from formalin (10%, 1 hour 30 mins), through graded ethanol (50%, 1 hour 30 mins; 70%, 1 hour 30 mins, 95%, 1 hour 30 mins, 95%, 1 hour 30 mins, 100%, 1 hour 30 mins) to xylene (2 buckets, 1 hour 30 mins each) to molten paraffin wax (2 buckets, 1 hour 30 mins each).

Tissue Processing with Domestic Microwave Oven
A domestic microwave oven (Sharp microwave oven, modelno: R207EK, powersource: 230- 240V, 50Hz, outputpower: 900W) was used in our study.The four glass beakers were filled with solutions, respectively, prior to processing the tissue in the microwave oven. Although the tissue samples were fixed in formalin at room temperature prior to the day of tissue processing, the tissue samples were still microwaved for two minutes in 10% formalin to make sure that the tissues were fixed adequately. The samples were then microwaved with a mixture consisting of equal quantities of 2-propranolol and acetone for dehydration. Xylene is used for the clearing process, and this is followed by waximpregnation.

A pilot study with 30 samples wascarried out to standardise the baseline timing for the procedure. The baseline timings were fixed at 2, 30, 5 and 25 minutes for tissue fixation, dehydration, clearing and wax impregnation, respectively.

The temperature of the solution is measured after each tissue processing step, and the microwave oven was left to cool for a couple of minutes before proceeding to the next step of the processing. A beaker containing an equal amount of distilled water was placed in the microwave throughout the four tissue processing steps to prevent overheating of the solution. For every step of tissue processing, fresh solutions were used.

All the reagents were heated directly in the domestic microwave oven except for the paraffin wax. The paraffin was melted separately on a hot plate prior to the wax impregnation processing step.

Table I depicts the protocols A, B and C with the time allotted (in minutes) of each stage of tissue processing accordingly.

Methods of Evaluation of Processed Slides
All the slides were evaluated by two experienced histopathologist without prior knowledge to which techniques were used to process the tissue samples. The morphological qualities of microscopic slides were analysed using light microscopy and a score of 1 (satisfactory) or 0 (unsatisfactory) were given to the slides. The parameters used for evaluation were the cytoplasm, nucleus morphology and staining characteristics. The slide was graded satisfactory if two or three parameters score 1 whereas it was graded unsatisfactory if none or only one of the parameters scored1. Table II provides the histological parameters along with its features to be graded for the morphological analysis.

RESULTS

A total of 80 tissue samples were processed in this study by both conventional method and three different microwave method. The tissue samples were divided into four groups equally, with 20 tissue samples per group. This is because previous literature such as Devi et al concluded that the morphological quality of tissue samples processed by domestic microwave oven wascomparable to tissue samples processed by a conventional method when the sample load in microwave oven was up to 25 samples.[5] In this study, 10% formalin is used for tissue fixation, propranolol with acetone is used for dehydration, xylene is used for clearing and paraffin wax is used for wax impregnation.

Muscular tissues which include both skeletal muscle and heart muscle tissue constituted to the highest percentage of tissues, together making 51.25% of the total samples and have the overall highest percentage of satisfactory slide among all the types oftissue.

The percentage of satisfactory slides of group 2 microwave protocol (Protocol A) is closely comparable to group 1 conventional group, as group 2 has an overall percentage of 80% where as group 1 has an overall percentage of 76.68%. Therefore, Group 2 microwave protocol is more suitable for tissue processing as compared to group 3 (Protocol B) and 4 (Protocol C). The morphological quality of tissue slides is best observed for microwave tissue processing protocol of group 2 with the tissue processing time of 62 minutes which is much better than group 3 and 4 microwave protocols, which have a tissue processing time of 70 min and 77 mins respectively and way better than group 1 conventional method, which has a tissue processing time of 18 hours. Where there's a difference in opinion, the two pathologists discuss and reach a consensus on the difference of opinion cases.

The morphological quality of histopathology slides of microwave protocol group 2 is superior as compared to group 1 (conventional method). This is shown through the average percentage of satisfactory slides, group 2 has a higher percentage compared to group 1. However, the morphological quality of histopathology slides of microwave protocol groups 3 and 4 is inferior as compared to group 1 (conventional method).

Groups 3 and 4 has 63.88% and 38.88% of slides that are graded as satisfactory and this is significantly lower compared to groups 1 and 2 which has 76.68% and 80% of satisfactory slides. The lower percentages of satisfactory slides in groups 3 and 4 is because the tissue samples processed in these groups showed a lot of degenerative changes. Among all the types of tissue processed, muscular tissues show much consistent results in all protocols whereas liver and spleen tissues show maximum degeneration in comparison to other tissues. Table III provides the summary and comaprision of morphological quality of the histopathology slides among the groups 1 to 4.

DISCUSSION

The total time for microwave tissue processing was increased gradually from 62 minutes to 70 minutes and 77 minutes.

Table I: Protocol for domestic microwave tissue processing

Microwave tissue processing (minutes)	Fixation-10% formalin	Dehydration-propanolol+ Acetone	Clearing-xylene	Wax impregnation
Protocol A	2	30	5	25
Protocol B	2	35	8	25
Protocol C	2	40	10	25

TableII: Rubrics for qualitative morphological analysis of histopathology slides [Devi et al][5]

Parameters	Features
Cytoplasm	Nuclear—cytoplasmic contrast; Eosinophilia of cytoplasm
Nucleus	Nuclear membrane; chromatin condensation; mitotic figures
Staining characteristics	Eosinophilic cytoplasm, nuclear cytoplasmic contrast, crisp staining of nucleus,

Table III: Comparison of percentage of satisfactory slides for each group

Type of tissue	Group 1 (Control)	Group 2	Group 3	Group 4
Liver	60%	0%	33.3%	0%
Kidney	66.7%	100%	50%	33.3%
Lung	66.7%	N/A	50%	50%
Skeletal Muscle	66.7%	100%	100%	100%
Heart	100%	100%	100%	50%
Spleen	100%	100%	50%	0%
Average %	76.68%	80%	63.88%	38.88%
Turnaround time	18 hours	62 mins	70 mins	77 mins

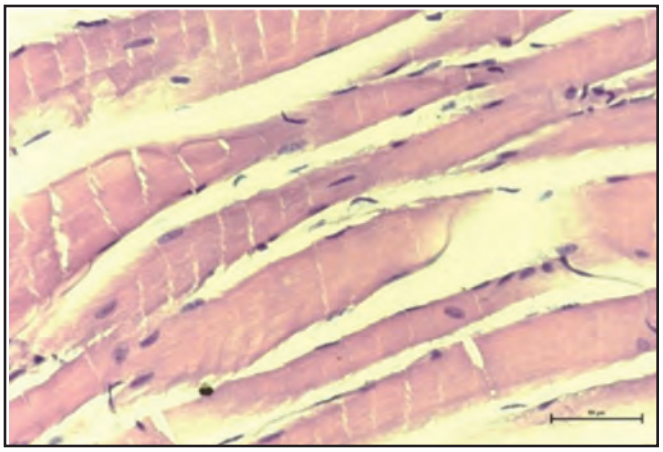

Fig. 1: Section of skeletal muscle from group 2

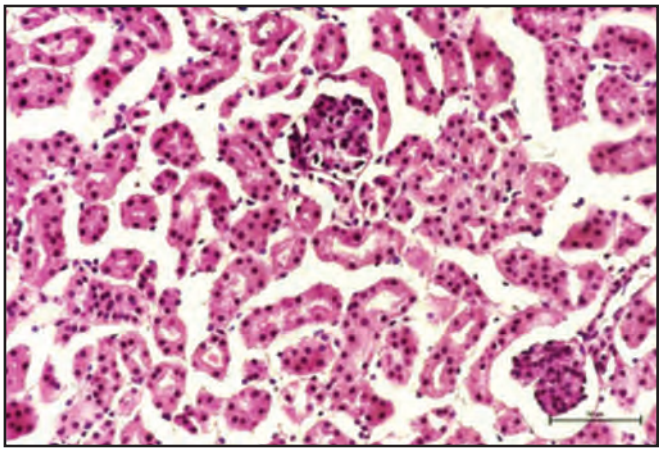

Fig. 2: Section of kidney from group 4

Tissue processing time in group 2 is 62 minutes which is much better than group 3 (70 minutes) and 4 (77 minutes), and way better than group 1, which has a tissue processing time of 18 hours. Group 2 also has the highest average percentage of satisfactory slides, therefore morphological quality of tissue slides is best observed when tissue processing time is 62 minutes.

The microwave power for fixation, dehydration and clearing tissue processing steps is fixed at 40 power for our domestic microwave oven used, whereas the microwave protocol for wax impregnation is fixed at 30 power for all microwave protocols. The microwave power is decided to be fixed at these powers through pilot study. When the microwave power is fixed at a power higher than 40, tissue is charred; however, if the microwave power is fixed at a power lower than 30, tissue is not able to process properly.

Groups 3 and 4 have a lower percentage of satisfactory slides as compared to groups 1 and 2 due to the degenerative changes shownby the tissue samples. The reason for tissue degeneration could be due to several factors. Firstly, the tissue samples came from a diverse sample group. These leftover animal carcases are used by other researchers prior to this research project. The conditions that the animals have gone through before sacrificing might be different with each animal carcase. Besides that, the duration that the animal carcase was left at room temperature before storage in freezer was unknown and time interval that the carcase stored in the freezer at the animal house facility was not able to be control as well. The microanatomy of the organs could also be one of the factors affecting the quality of slides. Liver and spleen tissues are highly vascular and have less connective tissue thus degeneration sets in faster if they were not properly stored in freezer or immediately fixed in formalin. Another

reason affecting the morphological quality of tissue slides could be due to the change in duration between protocols causing a variation in temperature when processing the tissue samples.

There were difficulties in taking paired tissue samples as the size of each animal were very small and it's quite impossible to divide the tissue samples into 4 equal sizes especially for the heart tissue and lung tissue. Besides that, the propranolol and acetone evaporated very quickly and aggressively during the microwave tissue processing process. As a result, the reagent had to be top up in the middle of the dehydration step to make sure all the cassettes are fully immersed in the solutions throughout the duration for properdehydration.

Gross sectioning is done in such a way that all the tissues samples obtained are of a similar size. This is because tissue samples of a larger size will need a longer time to be processed as compared to the smaller size tissue samples, and this will cause the smaller size tissue samples to be charred. Therefore, having a similar size of tissue samples will prevent any interference of the optimisation of the microwave tissue processing protocol.[5]

During the pilot study, the tissues were processed with a shorter duration for dehydration and wax impregnation. However, there is difficulty in cutting the tissues into thin sections as the tissues samples are not processed thoroughly and tissue samples are not properly dehydrated. In the initial part of trial study, the dehydration step of tissues is processed through only propranolol, which are the technique used by Rohretalin 2001; however, we noticed that the morphological quality of tissue slides processed through equal mixture of propranolol and acetone have a higher percentage of satisfactory score as compared to tissue slides processed through only propranolol.[6] Hence, we have decided to use both propranolol and acetone through out our microwave tissue processing protocol.We also noticed that atleast 25 minutes is needed for wax impregnation, which is slightly shorter compared to Devi et al, but slightly longer when compared to Kango et al, where he reported that the time for wax impregnation ranges from 5 minutes to 15 minutes.[5,7]

There was also difficulty in fixing the temperature of the microwave oven at one fix temperature as the domestic microwave oven that was used had limited control. Consequently, the temperature of there agent is measured manually at the end of each processing step, and this temperature is recorded throughout all theprotocols.

Our study has an overall tissue processing time of about 60 minutes (excluding tissue fixation, sectioning and staining of slides) when using domestic microwave oven for tissue processing. This is consistent with studies done by Panja et al, Kumar et al and Rohr et al and slightly longer when compared to the study done by Bond et al which has a microwave protocol of 42 minutes.[6,8,9,10]

The morphological quality of histopathology slides of tissues processed by automated tissue processor and domestic microwave oven in our study are very similar, with group 2 microwave protocol histopathology slides having as light superiority of quality as compared to group 1 conventional protocol. Likewise, Rohr etal and Bond etal also reported that the quality of histopathology slides of tissues processed by microwave protocol are more superior or similar to the tissues processed by conventional protocol.[6,10]

The same chemicals were used in our study and with study done by Devi et al in 2013 which was by using equal mixture of propranolol and acetone for dehydration and xylene for clearing instead of chloroform. However, Devi etal have a longer microwave tissue processing time (1 hour 46 minutes for a load of 20 samples) compared to our study. Nevertheless, both study has a similar result in the percentage of satisfactory slides.[5]

As a comparison between our research with other researchers from the table, we can see that the percentage of satisfactory slide of group 2 microwave oven tissue processing protocol is similar with other researchers such as Devi et al, Kumar et al and Kango et al in such a way that the percentage of satisfactory slides of tissue processed by domestic microwave oven is higher than that of tissue processed by automated tissue processor.[5,7,9] The reason why the result of our study is similar to these studies could be due to several reasons.

However, in the study done by Rohr et al, the percentage of satisfactory slide of conventional method is slightly higher than microwave method. This is also similar in our study when we compared the percentage of satisfactory slide of group 3 microwave protocol, which has a percentage of around 64% to group 1 conventional protocol, which has a satisfactory percentage of around 77%. In the study done by Rohr, he reported that the unsatisfactory result of microwave method was because the nucleus and cytoplasmic detail was unclear, and this might be due to inadequate tissue fixation in formalin and fatty tissue dropout whereas in our study, the unsatisfactory histopathology slides are mainly due to tissue degeneration of the samples.[6]

The percentage difference between microwave oven method and conventional method of tissue processing in our study and researcher Harsh Kumar study is also similar in a way as both project as a percentage difference of around 4% between the two methods.[9] All the studies mentioned above have used human samples and their results are comparable to our study.

The current study is limited by the usage of animal tissue and the number of samples processed. A larger number of samples and human samples of various types and sizes will provide more insight into the usage of the microwave-assisted tissue processing.

CONCLUSION

We concluded that we concluded that Group 2 microwave protocol is the most appropriate protocol (Protocol A) for tissue processing procedure when using domestic microwave oven (Sharp microwave oven, model no: R270EK). This is because the overall percentage of satisfactory slides inmicrowave protocol group 2 is significantly higher than microwave protocol groups 3 and 4. The morphological

quality of histopathology slides is best observed when the tissue processing time for microwave tissue processing is 62 minutes as compared to 70 minutes and 77 minutes. The quick tissue processing time for microwave tissue processing protocol increases efficiency and reduces both the cost of reagent use and patient anxiety. Histopathology slides of group 2 microwave protocol are closely comparable to histopathology slides of group 1 conventional protocol.

ETHICS APPROVAL

The study was approved by International Medical University Joint committee for ethics.

FUNDING

International Medical University Malaysia Authors' contribution: All authors had access to the data and an important role in writing the paper. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Gender differences in osteoporotic hip fractures in Sarawak General Hospital

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ABSTRACT

Introduction: Osteoporosis and osteoporotic fracture pose a major public health problem in our ageing population, and particularly concerning is the increased morbidity and mortality associated with osteoporotic hip fractures. While overall diagnosis and treatment for osteoporosis have improved, osteoporosis in men remains underdiagnosed and undertreated. We aim to describe the difference in clinical characteristics between elderly men and women with osteoporotic hip fractures in Sarawak General Hospital.

Materials and Methods: All patients diagnosed with osteoporotic hip fracture admitted to Sarawak General Hospital from June 2019 to March 2021 were recruited, and demographic data and clinical features were obtained.

Results: There were 140 patients with osteoporotic hip fracture, and 40 were men (28.6%). The mean age for males was 74.1 ± 9.5 years, while the mean age for females was 77.4 ± 9.1 years (p=0.06). The types of fracture consisted of neck of femur=78, intertrochanteric=61 and subtrochanteric=1. More men were active smokers (15% vs 1%, *p*<0.001). There were 20 men with secondary osteoporosis (50%), while 13 women (13%) had secondary osteoporosis (*p*<0.001). The causes of secondary osteoporosis among the men were hypogonadism, COPD, glucocorticoid-induced osteoporosis, renal disease, androgen deprivation therapy, thyroid disorder, prostate cancer and previous gastrectomy. There were two deaths among the men and four deaths among the women during the inpatient and 3 months follow-up period. There was no statistical significance between the mortality rates between male patients (5%) and female patients (4%) (*p*=0.55).

Conclusion: There were more females with osteoporotic hip fractures, and there were significantly more males with secondary osteoporotic hip fractures.

KEYWORDS:
Osteoporosis, hip fracture, secondary osteoporosis, gender difference

INTRODUCTION

Osteoporosis is an important public health issue globally, particularly in our ageing population. The main complication of osteoporosis is osteoporotic fractures, with osteoporotic hip fractures associated with increased morbidity and mortality. The rising cost of treatment of osteoporotic hip fractures will also result in an increased economic burden on healthcare systems. Cheung et al[1] studied the number of hip fractures in Asiaand projected the number of hip fractures in Asia will increase from 1,124,060 in 2018 to 2,563,488 in 2050, a 2.28-fold increase, with a rise in the direct cost of hip fractures increasing from 9.5 billion USD in 2018 to 15 billion USD in 2050, a 1.59-fold increase.[1]

While awareness of post-menopausal osteoporosis in women is increasing, along with developments in the treatment of the condition, male osteoporosis continues to be under-recognized and under-treated. There appears to be differences between male and female osteoporosis. The incidence of osteoporotic fractures in both men and women increased with ageing; however, in men the osteoporotic fractures happened about 10 years later than women.[2] The prevalence of osteoporosis in United States (US) men >50 years old was 3–6% whereas in women >50 years old it was 13–18%.[3] The biggest impact of osteoporosis is obviously the incidence of osteoporotic fractures, especially spinal and hip fractures. Hip fractures carry a high morbidity and mortality. For men, the incidence of hip fractures in the US ranged from 0.56 per 1000 patients per year at age 60 years to 13 per 1000 patients per year by age 85 years.[4]

Even though the prevalence of osteoporosis and osteoporotic hip fractures is higher in women, men seem to have a worse outcome and mortality after a hip fracture.[5] Haentjens et al[6] studied the excess mortality after a hip fracture in older men and women and concluded that older adults have a 5–8-fold increased risk for all-cause mortality during the first 3 months after a hip fracture.[6] Of particular interest is the fact that even though the excess annual mortality is high in both men and women, at any given age, the excess annual mortality post-hip fracture is higher in men compared to women.[6] The reason for the higher mortality in men after a hip fracture was likely due to men having more co-morbid conditions and men being older with more post-operative complications. Simunovic et al[7] reviewed the risk of death and post-operative complications among patients with hip fractures in fivestudies and found that hip fractures were associated with 14–36% 1-year mortality rate.[7] They also found that earlier surgery significantly reduced the risk of mortality.[7]

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During menopause, the abrupt loss of oestrogen causes rapid bone loss in menopausal women leading to an increased osteoporotic fracture incidence. Compare this with men, who experience a gradual decline in testosterone with ageing, resulting in gradual bone loss and subsequently having osteoporotic fractures almost 10 years later than women. The bone loss that increases with advancing age in men was demonstrated by the Osteoporotic Fractures in Men (MrOs) study, which showed that there was an increase in average bone mineral density (BMD) loss at the femoral neck with increasing age.[8] The authors of the MrOs also showed that lower BMD is associated with higher fracture risk in men; each standard deviation (SD) decrease in hip BMD increased the risk of hip fracture by 3.2-fold.[8] The age-adjusted annual rate of hip and nonvertebral fracture was 2.4 and 14 per 1000 person-years, respectively, on 4.4 years of follow-up.[8] The risk factors for low BMD and fractures in men are low weight, low physical activity, medications (selective serotonin reuptake inhibitors, anti-epileptic drugs) and medical conditions (abdominal aortic aneurysm, Parkinson's disease, poor renal function, chronic obstructive pulmonary disease, diabetes mellitus, diffuse idiopathic skeletal hyperostosis, certain ethnicity, vitamin D deficiency and hyperparathyroidism).

Secondary osteoporosis may be present in both men and women, but some studies stated that secondary osteoporosis wasmore common in men than women.[2] Identification of causes of secondary osteoporosis is useful as treatment of the underlying condition will usually improve the treatment of osteoporosis as well.[9] The most common causes of secondary osteoporosis are glucocorticoid excess, hypogonadism and excessive alcohol consumption. Other causes are gastrointestinal malabsorption syndrome, renal insufficiency, chronic respiratory disorders, rheumatoid arthritis, malignancy, anaemia, hyperthyroidism or excess thyroxine, hyperparathyroidism, anticonvulsants, smoking and immobilization.[10,11] Therefore, a careful history, physical examination and appropriate blood investigation (such as a full blood count, renal profile, liver profile, calcium, thyroid-stimulating hormone (TSH), 25-hydroxyvitamin D and testosterone) is needed during an evaluation of patients with osteoporotic risk factors and/or osteoporotic fractures.

The Malaysian hip fracture national registry in 2008–2009 from selected government healthcare facilities reported 510 cases of hip fractures, of which 165 patients were men (32%).[12] Trivial falls were the main mechanism of hip fractures.[12-14] The risk factors associated with osteoporosis were advanced age, certain ethnicity, the female gender, family history, low body mass index, sedentary lifestyle, smoking, alcohol, low calcium and vitamin D intake.[15] Malaysia would expect to have an increased incidence of osteoporotic fractures as life expectancy improves. Increased awareness about this condition will hopefully result in improved screening, diagnosis and treatment of the condition in both men and women.

We aimed to describe the gender difference in clinical characteristics in elderly patients with osteoporotic hip fractures in Sarawak General Hospital in this study.

MATERIALS AND METHODS

This was a prospective, observational study. This study, titled 'Osteoporotic hip fractures in Sarawak General Hospital' was registered in the Malaysian National Medical Research Register (NMRR) and received approval from the Malaysian Medical Research and Ethics Committee (MREC) (NMRR-19-323-46068 IIR) and was performed in accordance with the Declaration of Helsinki. All patients with osteoporotic hip fractures admitted to the Orthopaedics Ward, Sarawak General Hospital from June 2019 until March 2021 were recruited into the study after giving informed consent. A low trauma hip fracture is diagnosed as a presumptive osteoporotic fracture. Data regarding demographics, type of fractures, surgery, health co-morbidities, investigation results, dual energy x ray absorptiometry (DXA) and treatments were collected. All patients were assessed for causes of secondary osteoporosis clinically and additional blood investigations as necessary. All treatments for osteoporosis were according to the standard of care. The patients were subsequently followed up in the osteoporosis or geriatric clinics 3 months later, and further clinical data were collected among those who attended the clinics, including the death outcome. This study estimates the prevalence of male osteoporotic hip fracture is at 10%. With a margin of error of 5%, the minimum required sample was 138 based on a 95% confidence interval. This is quoted using Epi Info software by CDC.

Statistical analysis was performed using IBM SPSS Statistics version 25 software. Descriptive data areexpressed as mean ± SD. ANOVA is used for the comparison of means between groups. Categorical data are presented as frequency and percentage and analysed using Chi-square or Fisher's exact test. A value of $p < 0.05$ is considered statistically significant.

RESULTS

The demographics and clinical data of all patients are presented in Table I. There were 140 patients with osteoporotic hip fracture recruited in this study, with 40 male patients (28.6%). The mean age for males was 74.1 ± 9.5 years, while the mean age for females was 77.4 ± 9.1 years, and the difference was not statistically significant (p=0.06). The majority were non-smokers (77.9%). More men were active smokers compared to women (15% vs 1%, p<0.001). The ethnicity data did not show any statistical significance (p=0.49), but there seems be less Malay men compared to Malay women (12.5% men vs 21% women) among the patients with osteoporotic hip fractures, and more Bidayuh men compared to Bidayuh women (15% men vs 9% women) with osteoporotic hip fractures.

The co-morbidities that were present before the diagnosis of osteoporotic hip fracture were hypertension, diabetes mellitus, dyslipidemia, asthma, COPD, rheumatoid arthritis, malignancy, chronic kidney disease and thyroid disease (Table I). There were statistically significant differences between the number of men and women with diabetes mellitus (17.5% vs 41%, p=0.01), COPD (10% vs 2%,p=0.03) and chronic kidney disease (12.5% vs 3%, p=0.03). 65% of men and women had more than one co-morbidities (p=0.54). 15 women (15%) and 3 men (7.5%) had a previous osteoporotic fracture. Among those with a previous

Table I: Demographic and clinical data of patients with osteoporotic hip fracture

Clinical characteristics	Number of female patients (%), n=100	Number of male patients (%), n=40	*p* value
Number of patients	100(71.4)	40 (28.6)	n/a
Mean age	77.4 ±9.1 years	74.1±9.1 years	0.06
Ethnicity			
Chinese	58.0	22 (55)	0.49
Malay	21.0	5 (12.5)	
Iban	11.0	7 (17.5)	
Bidayuh	9.0	6 (15)	
Indian	1.0	0(0)	
Smoking history			
Non smoker	93.0	16(40)	**<0.001**
Ex smoker	6.0	18(45)	
Current smoker	1.0	6(15)	
Co-morbidities before fracture			
Hypertension	78.0	32(80)	0.79
Diabetes mellitus	41.0	7(17.5)	**0.01**
Dyslipidemia	38.0	16(40)	0.82
Asthma	3.0	0(0)	0.26
COPD	2.0	4(10)	**0.03**
Rheumatoid arthritis	3.0	0(0)	0.27
Malignancy	4.0	4(10)	0.17
Chronic kidney disease	3.0	5(12.5)	**0.03**
Thyroid disease	4.0	5(12.5)	0.82
Previous osteoporotic fracture	15(15)	3(7.5)	
More than one co-morbidity	65.0	26 (65)	0.54
Type of hip fracture			
Neck of femur	54.0	24 (60)	0.69
Intertrochanteric	45.0	16 (40)	
Subtrochanteric	1.0	0(0)	
Management of hip fracture			
Conservative management	21.0	15(37.5)	0.22
Proximal femoral nail antirotation (PFNA)	24.0	5 (12.5)	
Dynamic hip screw (DHS)	19.0	7(17.5)	
Thompson hemiarthroplasty	19.0	5(12.5)	
Total hip replacement (THR)	17.0	8 (20)	
DXA			
Mean neck of femur BMD	0.491(±0.10), n=21	0.583(±0.07), n=4	0.11
Secondary osteoporosis	13.0	20(50)	**<0.001**
Secondary osteoporosis detected after screening	2.0	7(5)	**<0.001**
Outcome			
Alive	96.0	38(95)	0.55
Dead	4.0	2(5)	

Table II: List of osteoporosis treatment started post-fracture

Treatment started post-fracture	Number of female patients (%), n=100	Number of male patients(%), n=40	*p* value
Treatment started post-fracture			
Calcium	100.0	40(100)	n/a
Vitamin D	100.0	40(100)	n/a
Bisphosphonates	34.0	6(15)	**0.03**
Denosumab	3.0	0	0.5
Patients still on active treatment	23.0	5(12.5)	0.26

Table III: Causes of secondary osteoporosis among all patients with osteoporotic hip fractures

Causes of secondary osteoporosis among female patients, n=13 , number (%)		Causes of secondary osteoporosis among male patients, n=20, number (%)	
Thyroid disorders	4(30.8)	Hypogonadism	6(30.0)
Rheumatoid arthritis	3(23.1)	COPD	4(20.0)
CKD/ESRF	2(15.4)	GIOP	3(15.0)
COAD	2(15.4)	CKD/ESRF	3(15.0)
Early menopause	1(7.7)	ADT	1(5.0)
Letrozole	1(7.7)	Thyroid disorders	1(5.0)
		Prostate cancer	1(5.0)
		Previous gastrectomy	1(5.0)

osteoporotic fracture, only seven were on calcium and vitamin D supplementation, while none were on bisphosphonate or denosumab.

Most of the patients sustained neck of femur fracture(55.7%) followed by intertrochanteric(43.6%) and subtrochanteric (0.7%). Surgical intervention was the mainstay of treatment in 74.2% while conservative treatment was administered in 25.7%. There is a trend of less men receiving surgical treatment after sustaining a fracture (37.5% men vs 21% women), but this is not statistically significant (p=0.22).

Only 21 patients had DXA scans performed (17 women and 4 women). The mean neck of femur BMD was 0.491(±0.10) in women and 0.583 (±0.07) in men (p=0.11).

The treatment started during admission post-fracture is presented in Table II. All patients received calcium and vitamin D on admission, while bisphosphonate and denosumab were started during follow-up. Forty patients received bisphosphonate while three patients received denosumab. However, many patients defaulted follow-up, and only 23 women (23%) and 5 men (12.5%) are still on active follow-up. Among those who defaulted follow-up, the average duration of treatment was 2.60 months (±3.65).

The secondary osteoporosis causes that were identified among all patients were COPD, hypogonadism, thyroid disorders, chronic kidney disease (CKD)/End stage renal failure (ESRF), glucocorticoid-induced osteoporosis (GIOP), rheumatoid arthritis, androgen deprivation therapy (ADT), asthma, early menopause, aromatase inhibitor therapy, malnutrition from previous gastrectomy and prostate cancer. 50% of the male patients had an identifiable causes of secondary osteoporosis, while only 13% of the female patients had secondary osteoporosis (p<0.001). After screening for secondary osteoporosis, 5% of men and 2% of women were discovered to have an identifiable cause of secondary osteoporosis (p<0.001) (Table I). The serum calcium result was available for 131 patients (95 women and 36 men), and the mean serum calcium level was 2.26 (±0.13) mmol/L in women and 2.28±0.17 mmol/L inmen.

Table III shows the causes of secondary osteoporosis in both men and women. The main causes of secondary osteoporosis in men were hypogonadism (30%) followed by COPD, GIOP and CKD.

During the inpatient and 3-month follow-up period, twomen and fourwomen died. Four patients died during admission, while two patients died during the 3-month follow-up period. Three patients died from sepsis, while one patient died from COAD. There was no statistical significance in the mortality rates between male patients (5%) and female patients (4%) (p=0.55). The mortality rate between those who underwent surgery (2.9%) and those who opted for conservative treatment (8.3%) was not statistically significant (p=0.6).

DISCUSSION

Even though we are facing an ageing population with an expected rise in cases of osteoporotic hip fractures, there is still poor awareness regarding osteoporosis. Male osteoporosis, being less common than female osteoporosis, continues to receive little attention in terms of screening, diagnosis and treatment. This can hopefully be remedied by increased clinical data in the field of osteoporosis. The Malaysian clinical guidance for the management of osteoporosis included some data regarding the incidence and treatment for male osteoporosis.[16] Data from other Asian countries are available as well, with the Asian Osteoporosis comparing hip fracture data from Hong Kong SAR, Singapore, Malaysia and Thailand (Chiang Mai) in 1997.[17] The study reported the age-adjusted incidence rate for men and women as follows (per 100,000): Hong Kong 180 and 459, Singapore 164 and 442, Malaysia 88 and 218, Thailand 114 and 289; compared with US Whites 187 men and 535 women. In our study, the incidence of male osteoporotic hip fracture was 28.6%, which was similar to other studies. In our study, as expected, the proportion of women with osteoporotic hip fractures outnumbered the men. Both groups have a mean age of >70 years. However, there was no statistically significant difference in mortality rates among the men and women in our study. This may be due to both groups being in the elderly group with co-morbidities.

Our current study showed that 50% of our male patients and 13% of female patients had secondary osteoporosis. This finding is consistent with reported data that 30% of post-menopausal women and 50–80% of men were found to have secondary osteoporosis.[18] It is worthwhile to consider secondary osteoporosis, as the treatment may be different for certain underlying conditions, and certain conditions and medications may need bone health issues to be addressed.[18] Ryan et al[19] examined 234 men diagnosed with osteoporosis via DXA and measured 25-OH-vitamin D, testosterone, luteinizing hormone, follicular stimulating hormone (FSH), thyroid stimulating hormone (TSH) and spot urinary calcium-to-creatinine.[19] 75% had secondary osteoporosis including hypogonadism, vitamin D deficiency, hypercalciuria, subclinical hyperthyroidism and hyperparathyroidism.[19] The authors showed that with history, physical examination and basic laboratory investigationswill help to identify osteoporotic men with secondary osteoporosis.[19] Colangelo et al[20] proposed that after history and physical examination, a first-level laboratory test of full blood count, erythrocyte sedimentation rate (ESR), serum calcium, phosphorus, creatinine, alkaline phosphatase, total protein with electrophoresis and a 24-hour urinary calcium should be performed.[20] Other laboratory investigations such as ionised calcium, parathyroid hormone (PTH), 25-OH-vitamin D, TSH, dexamethasone suppression test, serum and urinary immunofixation, anti-transglutamase antibodies, testosterone in men, serum tryptase and ferritin, should be considered clinically if indicated.[20]

There were three men on glucocorticoids and one man on androgen deprivation therapy (ADT) in our study. Patients on these medications are recommended for osteoporosis evaluation (including Fracture Risk Assessment Tool (FRAX), BMD), calcium and vitamin D supplementation and treatment with bisphosphonate, denosumab or teriparatide as appropriate.[20] Adler et al[21] examined 115 men on ADT referred for DXA and found 33% would need osteoporosis treatment. Clinicians should be more aware of osteoporosis evaluation when prescribing medications such as ADT and glucocorticoids.

There has been much development in the treatment of post-menopausal osteoporosis, but data for male osteoporosis treatment are notable as well. There is less evidence for the treatment efficacy of male osteoporosis due to the smaller number of male participants compared to women in clinical trials. Evidence-based treatments for male osteoporosis are bisphosphonates (alendronate, risedronate, zoledronic acid), denosumab and teriparatide.[22-28] There is compelling evidence that current osteoporosis treatment is equally effective in men and women, not only to increase BMD but also to prevent osteoporotic fractures.[29] Effective treatment for GIOP for men and for male osteoporosis on ADT includes bisphosphonates, denosumab and teriparatide.[26,30-31] Testosterone replacement is indicated for symptomatic hypogonadal men, but data on its efficacy for fracture prevention arelacking. Thus, additional osteoporosis treatment may be needed, especially in men with very low testosterone who are at high risk of bone loss and/or men not able to receive testosterone replacement.[32]

However, there still exists a treatment care gap between men and women. The Canadian Multicentre Osteoporosis Study found that between 1996 until 2002, 90% of men with fragility fractures remained undiagnosed and untreated for osteoporosis.[33] Yeap et al[34] found that following a hip fracture, only 36.8% of patients (men and women) received treatment, but out of these, 24.2% were on calcium and vitamin D only.[34]

There is a need to increase awareness of male osteoporosis among clinicians, so a diagnosis is made, and appropriate treatment administered, especially among those with fragility fractures and those at risk of secondary osteoporosis. There are guidelines that recommendbone health assessment, obtaining DXA and FRAX in those at risk of osteoporosis, and starting appropriate treatment.[35,36] The Canadian Osteoporosis Society recommends screening men >65 years old for osteoporosis, while the National Osteoporosis Foundation and International Society for Clinical Densitometry and the Endocrine Society recommend screening all men >70 years old or men aged 50-69 years old with risk factors.[36] Alswat et al[37] analysed the rate of osteoporosis screening between men and women in primary care, and men had a screening rate of 18.4% compared to females screening rate of 60%.[37] De Martinis and colleagues[38] also highlighted the gender bias in osteoporosis screeningand found that among those referred for osteoporosis screening at their centre, 94.5% were women while only 5.4% were men. They also found that men were under-screened for osteoporosis, exhibited secondary osteoporosis more frequently and had a higher calculated risk for hip fractures compared to women.[38]

LIMITATIONS

The death outcome was collected at inpatient and at 3-month follow-up visit only. This may not reflect the 1-year mortality rate. The difference in mortality rates between those who had surgery and those who opted for conservative treatment is likely affected by this factor as well. Data collection was temporarily halted during the height of the Coronavirus Disease 2019 (COVID-19) pandemic as the fracture liaison services were temporarily stopped. The number of cases in this study may not reflect the true incidence of male osteoporotic hip fractures. Some investigation results were not available for the secondary osteoporosis screening, and the number of secondary osteoporosis may not be truly reflected. Some patients may have been treated in private healthcare facilities, and our patient cohort may not be reflective of the population in Kuching and its surrounding areas.

CONCLUSION

The gender differences in osteoporotic hip fractures in the elderly are the increased proportion of women compared to men, and men havesignificantly increased incidence of secondary osteoporosis. Men had more CKD and COPD, and more men were smokers, while more women had diabetes mellitus. There does not seem to be a difference in mortality rates between men and women in this study. Clinicians should be more aware of the importance of screening, diagnosis and treatment of osteoporosis, especially in the context of an ageing population.

ETHICS APPROVAL

This study received ethics approval from the Malaysian Medical Research and Ethics Committee (NMRR-19-323-46068 IIR).

INFORMED CONSENT

All participants in this study provided informed consent to participate.

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COMPETING INTERESTS

The authors declare that they have no competing interests inthis study.

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Rejuvenating multiple true–false: Proposing fairer scoring methods

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ABSTRACT

Introduction: Multiple true–false tests (MTF) with penalty scoring consistently delivered low scores and many failures for over two decades in our medical faculty. This issue remained unaddressed, as the overall student performance was redeemed by other assessments like Best Answer Questions and Modified Essay Questions. The post-test item analyses revealed that there were several items with unacceptable difficulty index and discrimination index, many omissions, and that the false options performed worse than the true options in the difficulty index but better in the discrimination index. This study aimed to evaluate some final professional examination MTF papers to propose possible remedial measures.

Materials and Methods: We examined 5 years' final professional examination MTF results, their item analysis, the student performance in true and false items and failure rates.We explored the impact of excluding the flawed questions post-test based on item analysis and redoing the scores. We also explored the effect of removing the penalty scoring and recalculating the scores.

Results: The two new scoring methods, such as post-weeding recalculation and no-penalty proportionate scoring, showed remarkable improvement in scores and also reduced the failure rates significantly compared to the penalty-scoring model.

Conclusion: We propose two new scoring methods for MTF, which would be fairer to the students and would have the prospect of rejuvenating MTF tests.

KEYWORDS:
MTF with no penalty scoring, multiple true–false, post-test weeding, MTF scoring methods

INTRODUCTION

The American National Board examinations scrapped Multiple True–False (MTF) tests, as it was not considered suitable to test higher knowledge than recall of facts.[1] However, this notion was disputed.[2] MTF is still used widely in other parts of the world.[2-5] MTF was considered superior to One Best Answer Questions (OBA or BAQ), because it could test five individual items of knowledge in one question.[2-4,6-8] Other advantages attributed to MTF were it could accommodate complex scenarios[6]; it could test minute understanding of students[9] and it allowed extensive feedback to students that could stimulate learning.[3,10] Factual knowledge is essential for a doctor to function efficiently, and MTF is the best at testing it.[2,3,7,11-13] The ability to discriminate false statements from true, which is required of doctors, is well-tested in MTF.[2] Omission is not an option in real-life clinical situations, and so, it should not be allowed in MTF also.[14] Omission is eliminated in the no-penalty or number-right scoring model. Most criticisms against MTF could be traced to attempts at testing higher knowledge than recall of facts, flaws in the questions and inadequate vetting of questions.[2,3,7,10] Construction of flawless MTF questions, thorough multidisciplinary vetting, post-test analysis and feedback to the question authors were considered very important for quality assurance.[1,6,15] Getting feedback from the examinees about the questions could be a valuable measure to improve the standard of MTF.[3] MTF performance should correlate well with the performance of other theory assessments, and poorly performing questions should be dropped from the question bank.[1,6,16] OBA also is not free from the guessing issue, and it might overestimate the students' knowledge.[9] Some studies reported the poor correlation of MTF with other theory assessments and the better performance of OBA.[10,15]

How to score MTF is a disputed issue. Kanzow et al.[6] described over a dozen penalty scoring algorithms, each of which produced different scores on the same test and concluded that none of them was worth recommending. Similarly, Schmidt et al.[14] described over two dozen scoring methods. However, none of them was shown as universally conclusive. Some studies advocated the abolition of the penalty scoring[12,13], while some advocated keeping it.[3,5,7] MTF without penalty scoring would reduce score variability and attenuate discrimination between examinees.[13] Many universities have adopted the no-penalty scoring system, where the correct responses are given points, and the incorrect responses and omissions are ignored.[12,13] The possibility of scoring at least 50% by blindly answering all the items as true in the no-penalty model remains unresolved.[13,17] The penalty scoring led to many items being left unattempted and low scores in MTF in our institution. The same pattern was repeated in almost all minor and major examinations of the faculty for over two decades. In one of our previous studies, we argued that the inherent flaws in MTF could not be remedied, as fewer false (F) options were answered correctly and omitted

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more often than true (T) options.[17] Good F options were harder to construct, but they had a better discrimination index, meaning more higher performing students answered them correctly.[16,17] Since MTF with and without penalty scoring have unresolved issues, we explored ways to uplift both of them.

This study was triggered by the observation of the consistent poor performance of medical students in MTF papers. Our faculty used penalty scoring in the 5-option MTF tests in which each correct answer got 1 point, each incorrect answer got –1 point and '0' point for omission. The negative marks were not carried over from one question to the next. The poor performance in MTF was attributed to the penalty scoring. Furthermore, MTF was always used along with BAQ and MEQ, which covered up the issue. Our previous studies revealed that the flaws in the questions, especially the careless construction of false items, contributed to this issue,[17] and that the MTF performance in the final professional examination (FPE) adversely impacted the final scores and grades of the graduates.[18] In this context, we explored the feasibility of rejuvenating MTF with new scoring methods for penalty-MTF and no-penalty MTF, which would consider the flaws in the tests and also make MTF fairer for the students.

MATERIALS AND METHODS

This study was conducted in a public university in Malaysia with formal approval by the faculty's dean and the ethics committee of the university. We examinedthe data from five FPEs (A,B,C,D,E),which used 60 five-option MTF questions as one of the three theory papers.

Data Preparation

The original penalty-MTF scores were noted from five FPE results. The distribution of T and F items was noted. Students' optical mark reader (OMR) reports were checked to get the number of T items and F items answered correctly. The total of these served as the no-penalty scores. The number of omissions in each question was also noted.We studied the pass/fail rates in the three sets of scores. The three sets of scores obtained by the three scoring methods were compared and statistically analysed.

The three scoring methods and sets of scores we compared were:

1. The original one with penalty scoring, as practised in the faculty
2. The post-weed: scores recalculated after weeding the flawed questions from the original (recalculation was done by the OMR machine). Flawed questions include (a) those incorrectly answered by 60% or more students (difficulty index (DIFI) of <0.4); (b) questions with 40% or more omissions; (c) those with 0 or negative discrimination index (DISI)
3. With no-penalty scoring: the scores were noted from the OMR reports, which provided the T and F items answered correctly.

The pass score for all the sets was 50%. The no-penalty set had an additional criterion, which aimed to offset the possibility of scoring by blind guessing in future tests: there should be a minimum score of 20% from F items and 20% from T items. If either F or T score was less than 20%, for each two correct F, 3 T would be counted. If both the F and T scores were 20% or more, all correct F and T items would be counted.

Data Analysis

All the data were captured in Microsoft Excel and then transferred to IBM SPSS for analysis. The mean percentage scores of the original MTF tests, post-weed scores and no-penalty scores were compared with a dependent (paired) sample t-test. This test aimed to examine the mean difference between the original scores versus the post-weed scores and the original scores versus the no-penalty scores. We calculated the Cohend to examine the practical significance (effect size). Apart from this, we also categorised the scores into 'pass' and 'fail' of the three sets. A non-parametric Cochrane Q test was done to obtain the statistical difference among the three sets. A p value of less than 0.05 was considered statistically significant.

RESULTS

Table I illustrates the descriptive statistics of the students' original MTF scores with penalty, post-weed scores and scores with no penalty from the five FPEs. Data analysis revealed that the mean difference between the original and post-weed varied from 2.58 percentage points to 5.43 percentage points. The percentage score differed substantially between the original and the no-penalty category, which ranged from 11.36 percentage points to 14.04 percentage points. The year-wise paired sample t-test indicated a statistically significant difference in the penalty scores versus post-weed scores (p<0.001) with large Cohend. Similarly, a statistically significant difference was found between penalty scores versus no-penalty scores (p<0.001), and the effect size was large.

Table II illustrates the students' pass/fail rates resulting from the three scoring methods. The passing rate in MTF with penalty was very low. It varied from 15.2% to 28%. The passing rate improved with post-weed recalculation, which varied from 25.9% to 49.2%. In MTF without penalty, the passing rate was substantially higher. It varied from 70.8% to 89.3%.

Five hundred and eighty-five students' scores were examined to determine the pass rate changes with three scoring methods. Cochrane's Q test determined that there was a statistically significant difference in the proportion of students who passed the tests, $\chi^2(2) = 556.480$ (2), $p < 0.001$ (Figure 1). A post-doc pair-wise analysis revealed that there was a statistically significant difference between penalty MTF versus post-weed (test statistic=.142, p<0.001), similar to penalty MTF versus no-penalty MTF (test statistic=.592, p<0.001). The test also showed that there was a statistically significant difference between post-weed and no-penalty MTF (test statistic=.452, p<0.001).

Table III demonstrates the trends in T and F distribution and the students' performance in the five tests. The proportion of true items was more than false items in a 55:45 ratio; about 65% T items were answered correctly, while only about 46% F items were answered correctly. The omission rate varied from 24.1 to 29, with a mean of 26.8% (Table III).

Table I: Mean MTF scores obtained with three scoring methods

FPE	N	Scores with penalty Original - Post-weed				Mean difference	Cohen-d	No-penalty scores		Mean difference	Cohen-d
		Mean	SD	Mean	SD			Mean	SD		
A	112	41.79	7.48	44.37	8.02	2.58	2.32	55.57	7.34	13.78	1.38
B	118	45.79	6.84	50.04	7.34	4.25	4.02	57.14	7.23	11.35	15.50
C	122	44.70	6.73	47.93	6.83	3.23	3.10	58.74	7.06	14.04	3.49
D	106	42.28	7.86	47.71	8.53	5.43	3.14	54.59	8.41	12.31	3.89
E	127	43.83	7.51	47.04	7.78	3.21	2.78	56.35	7.62	12.52	3.15

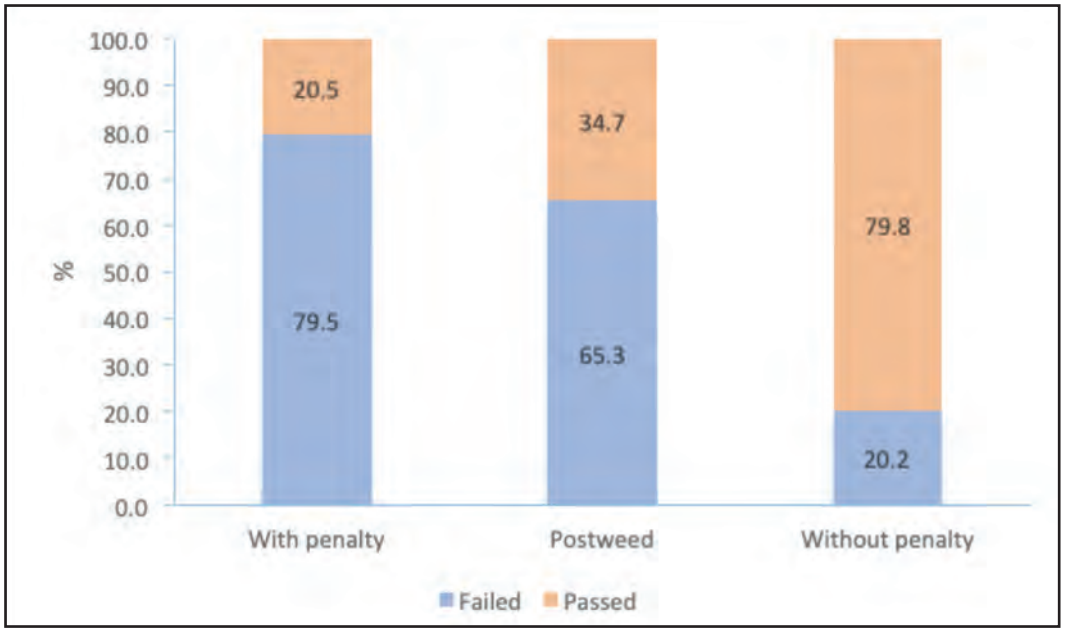
Statistical test obtained from paired sample t-test (Score with penalty vs Post-weed) and (Score with penalty vs score without penalty)
Cohen d = 0.2, 'small', 0.5 = 'medium' and >0.8 'large' effect size.

Table II: Pass/fail rates with 50% cut-off obtained with three scoring methods

FPE	With penalty Original				With penalty Post-weed				Without penalty			
	Fail		Pass		Fail		Pass		Fail		Pass	
	n	%	n	%	n	%	n	%	n	%	n	%
A	95	84.8	17	15.2	83	74.1	29	25.9	23	20.5	89	79.5
B	85	72.0	33	28.0	60	50.8	58	49.2	25	21.2	93	78.8
C	96	78.7	26	21.3	79	64.8	43	35.2	13	10.7	109	89.3
D	87	82.1	19	17.9	71	67.0	35	33.0	31	29.2	75	70.8
E	102	80.3	25	19.7	89	70.1	38	29.9	26	20.5	101	79.5

Table III: True and false item distribution and scoring in five MTF tests

FPE	Distribution		Omission %	Answered correctly	
	T (%)	F (%)	Mean and (Range)	T% (Range)	F% (Range)
A	54.7	45.3	27.2 (3–46.67)	64.6 (81–44)	44.7 (78–22)
B	54.0	46.0	26.5 (3.33–48)	63.7 (83–39)	49.5 (74–30)
C	53.3	46.7	24.1 (0–43.67)	67.9 (87–48)	48.0 (73–30)
D	56.3	43.7	29.0 (7.33–52.67)	62.8 (84–46)	44.1 (69–21)
E	58.7	41.3	27.4 (6.98–43.49)	64.9 (88–45)	44.2 (89–34)
Mean	55.4	44.6	26.8 (0–52.67)	64.8	46.1



Cochran's Q test (df)= 556.480 (2), p < .001
Fig. 1: Overall pass/fail rates in MTF with three scoring methods

DISCUSSION

Test reliability improves with test length, and MTF being easier to construct would make it possible to include more items, which would broaden the subject coverage.[19] Penalty scoring leads to omissions, which narrows the score distribution and lowers the test reliability.[19] With no-penalty scoring, the issue of guessing would be mitigated, and the validity and reliability of the test would improve by increasing the number of items.[20] MTF being easier to construct and allowing to test more facts than BAQ and extended matching question (EMQ), we find it worth rejuvenating it with new scoring methods, which would make it fairer to the students and viable to use no-penalty scoring. The issue of blind guessing seems to be ignored generally with no preventive measures suggested even in the 27 MTF scoring methods described in a systematic review article published in 2021.[20] In our setting, the general tendency has been to blame the students for their low MTF scores and ignore the quality of questions as a possible contributing factor. One of our previous studies discussed this issue.[16] The expert vetting would have passed the questions as 'perfect', but the post-test item analysis revealed the flaws in the questions. The rate of omission, DISI and DIFI were considered while recruiting questions for question bank,[16] as these indicators are considered valuable to judge the quality of the items. Standard error of measurement is lowered, and test reliability is reduced if the test contains very easy or very difficult items.[20] If some of the items were not suitable for further use, how could they be suitable for the current use? This concept led us to weed out flawed questions post-test and adjust the scores to benefit the students. We chose a DIFI of <0.4 and a DISI of ≤0 as cut-off points for exclusion of questions for score recalculation. In no-penalty model, guessing is permitted, and scores are higher as omission is eliminated.[20] Our results showed a consistent pattern of scores improving with the weeding of flawed questions and with no-penalty scoring (Tables I and II; Figure 1). Both of them showed the potential to rejuvenate the MTF tests.

MTF is the only test with penalty scoring. The fear of penalty leading to many omissions and the penalty-scoring leading to loss of scores were the apparent reasons for the poor scoring and the high failure rates in MTF. There is no reason for applying a penalty other than to prevent blind guessing. Moving to no-penalty scoring, we needed to devise an alternative method to preclude blind guessing, as students would know by experience that more than 50% of the items might be true. So, why not just answer all the items as true! In the absence of penalty, such a trick would secure as many scores as the number of T items in the paper. Discarding penalty scoring without any safeguards against blind guessing would be unwise. To surmount blind guessing, we have proposed a minimum score of 20% each for both F and T items and a proportionate scoring of T:F::3:2. This was based on our finding that in the five MTF papers the T and F ratio was approximately 55:45, and the mean of F items answered correctly was 46.1% (Table III). In the absence of 20% F scores or T scores, the score would be calculated in a proportion of 2:3::F:T. This is based on the proportion of correctly answered F and T items in five FPEs (Table III). If the F and T scores both exceed 20%, no restrictions would apply. In the 5 years' results, none of the students scored less than 20% in either F or T items (Table III). This could be explained as these scores were calculated without penalty, after the tests were done in the penalty scoring mode. Only when the faculty moves from penalty to no-penalty MTF, this proposal could be validated. It would also be wise to include Extended Matching Questions, Short Answer Questions or Very Short Answer Questions to broaden the assessment.

LIMITATIONS

We could not use authentic no-penalty MTF, as our faculty did not practise it yet. Therefore, the new scoring method for no-penalty MTF could not be validated. The no-penalty scores we used for this study were derived from original MTF tests with penalty. We removed the negative scores deducted as penalty to get the no-penalty scores. In this method, the scores could be slightly lower than the actual no-penalty MTF, as omission would be eliminated in no-penalty tests.

CONCLUSION

We are facing the prospect of a valuable assessment tool like MTF withering away, as the student scores are consistently low in these tests. It is worth rejuvenating MTF, as it has several pluses. We propose post-weed score recalculation for the penalty-scoring MTF and a minimum F and T passing score with a proportionate F and T scoring method for the no-penalty scoring MTF.

CONFLICTS OF INTEREST

None of the authors declared any conflict of interest.

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ETHICAL APPROVAL

Ethical approval was obtained from the Ethics Committee (UNIMAS/TNC(PI)/09-65/01(47) RUJUKAN ETIKA: FME/22/39 of Universiti Malaysia Sarawak (UNIMAS). We also obtained administrative approval from the dean of the Faculty of Medicine and Health Sciences.

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ORIGINAL ARTICLE

A nationwide, multihospital, cross-sectional, self-reported study: Knowledge, attitude and behaviour concerning the use of personal protective equipment among healthcare workers during the COVID-19 pandemic in Malaysia

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ABSTRACT

Introduction:Personal protective equipment (PPE) is crucial in reducing the risk of hospital-acquired COVID-19 as health care workers (HCW)s are highly exposed to the virus during the management of patients with COVID-19. This study assesses the knowledge, attitude and behaviour of the HCWs towards the use of PPE during the COVID-19 pandemic in Malaysia.

Materials and Methods:This is a nationwide, online-based cross-sectional study utilising a self-administered questionnaire that was distributed to tertiary hospital HCWs in Malaysia, conducted between June and August 2020.

Results: Forty-eight physicians, 66 nurses and 79 medical assistants participated in this study. 73.6% correctly recognised PPE components while 40.4% revealed correct hand hygiene practices and approximately 20% had misconceptions about the proper usage of PPE. Although 78.8% disclosed high compliance, 37.3% perceived that PPE protocol interferes with patient care. HCWs have suboptimal knowledge levels of hand hygiene. Age and poor behaviour were the independent predictors of good compliance with PPE.

Conclusion: This study highlights the necessity to analyse discrepancies in PPE practice among HCWs and its contributing elements. Recognised barriers should be addressed to narrow the gap between knowledge, attitude and behaviour to improve compliance. The study findings would assist in developing an improved disease transmission control and prevention training protocols for HCWs as a preparation for possible infectious outbreaks in the future.

KEYWORDS:
COVID-19; personal protective equipment; health care worker; infection prevention; knowledge, attitude, and behavior

INTRODUCTION

In December 2019, the first case of a highly infectious pneumonia caused by coronavirus was confirmed in Wuhan, Hubei province, China. The disease was later named the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Subsequently, the virus spread to over 200 countries. The World Health Organization (WHO) declared it as a pandemic in March 2020.

The initial cases were discovered in Malaysia in January 2020.[1] From January 2020 to May 2021, fatalities due to COVID-19 among health care workers (HCW)s continued to increase with an estimated 80,000–180,000 deaths recorded by the WHO.[2] In a study conducted at a Malaysian teaching medical centre in 2020, the prevalence of COVID-19 infection among HCWs was 0.3%.[3] However, as of 31 August 2021, nearly 20,000 HCWs in Malaysia had been infected, with a fatality of 0.09%.[4] Hospital-acquired infections constituted 40% of cases among the health work force with 20% from HCW interaction, 10% transmission from patients and 10% from various unidentified causes.[5]

The complex network of disease transmission between HCWs, patients and the community is a major threat to the healthcare systems due to the highly transmissible nature of the virus. The surge in HCW infections results in the reduction of hospital resources that can potentially incapacitate the healthcare system. To prevent the catastrophic collapse of the health care system, it is essential to protect HCWs from contracting nosocomial infection.[6,7] Consequently, HCWs are required to wear proper personal protective equipment (PPE) to protect themselves and their patients. Evidence has clearly demonstrated the importance of PPE in a study undertaken by Liu et al. where HCWs who used proper PPE did not contract the infection despite being highly exposed to COVID-19.[8] This corresponds with research conducted by Burke et al. who discovered that when proper PPE was used, the risk of contracting infections during patient care among HCWs was significantly lower compared to those who did not wear PPE.[9] The CDC, the WHO, as well as the Ministry of Health Malaysia have outlined clear and easily accessible guidelines on the appropriate levels of PPE for various activities and procedures during the management of COVID-19.[10-12] Proper PPE usage is essential in preventing the spread of COVID-19, thus the need to study the knowledge, attitude and behaviour towards the use of PPE among HCWs at tertiary hospitals in Malaysia.

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MATERIALS AND METHODS

Study Design and Setting

This is a cross-sectional study designed to cumulate the information on knowledge, attitude and behaviour of PPE use among HCWs in Malaysia. HCWs from tertiary public hospitals under the Ministry of Health who provided consent were included in this study. At the time of study, there were 37 tertiary hospitals under the Ministry of Health Malaysia.

Data Collection Instruments and Procedure

This study was conducted between the second and third wave of COVID-19 in Malaysia, prior to the availability of vaccination. Data were collected using a self-administered online questionnaire (Google form) in English from June 2020 to August 2020. The link to the questionnaire was shared via email and WhatsApp to physicians, nurses and medical assistants through hospital administration offices of the 37 tertiary centres following the approval of the Medical Research and Ethics Committee, Ministry of Health Malaysia. Minimum sample size of 196 was calculated according to the formula $n=Z^2P(1-P)/d^2$ with the assumption of a total population estimate of 10,000 HCWs employed at tertiary hospitals, 95% confidence interval (Z=1.96), expected prevalence (P) of 0.5 and d=0.05.[13]

The questionnaire was adapted from a study conducted by Daugherty et al. (2009)[14], comprising a section on demographic information, six items on knowledge, eight items on attitude and three items on behaviour.[13] In the knowledge section, we classified good and poor knowledge levels based on Bloom's cut-off point of 80%–100%. One point was awarded to each correct answer, while incorrect response was scored as zero. A score of ≥ 5 was set as good PPE knowledge. Attitude and behavioural aspects of PPE were elicited by a 5-point Likert scale (e.g., completely agree, agree, neither agree nor disagree, disagree, completely disagree). Good attitude and behaviour were defined as responses that indicate agreement or complete agreement in all questions. For the level of compliance to PPE, we considered responses with self-reported compliance of > 80% as high (good) compliance. In a work by Berhe et al.[15] on the control of nosocomial infections, 'high compliance' was specified as > 80%.

Data Analysis

A statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 25.0. All five-point Likert-scale responses were then categorised into completely agree/agree versus neither agree nor disagree/disagree/completely disagree. A further statistical test was performed to analyse the relationship between the variables. The statistical significance level was set at $p<0.05$. Categorical variables were compared with Chi-square test. Pearson correlation test was done to determine the relationship between continuous variables. The odds ratio (OR) was estimated based on both univariate analysis and multivariate logistic regression analysis for the determination of independent predictors for high compliance with the PPE used during patient care. Variables such as characteristics of HCWs, knowledge, attitudes and behaviours were included in the model using stepwise conditional forward and backward entry, if $p<0.1$ in a univariate analysis. An OR less than 1 indicated low compliance towards the use of PPE, while an OR greater than 1 indicated high compliance with PPE during patient care.

RESULTS

Respondent Characteristics

Table I illustrates the characteristics of the respondents. A total of 193 respondents participated in this study with 46.1% males and 53.9% females. The mean age of the respondents was 30.6 with a standard deviation of 5.85 years. Physicians comprised 25.7% of the respondents, while 34.2% were nurses and 40.9% were assistant medical officers. Most respondents were emergency and trauma department (ETD) personnel (67.9%), 11.9% were from the infectious disease unit and 20.2% were from other departments. Slightly over three-quarters (79.3%) were directly involved in the care of patients with COVID-19.

Knowledge

The majority of the respondents (73.6%) managed to correctly identify the appropriate PPE (Table II). Good knowledge in the usage of the suitable face mask, and proper protective eyewear and gown was demonstrated in 79.8% and 80.3% of HCWs, respectively. In addition, only 40.4% possessed adequate knowledge and understanding of hand hygiene with a significantly lower percentage of nurses and medical assistants scoring correct responses for the mentioned item questions ($p<0.001$). No significant difference in the total knowledge scores was found between physicians, nurses and medical assistants.

Attitude

In this study, 90.2% believed that proper PPE use conferred sufficient protection against COVID-19 infection among HCWs, with significantly more nurses possessing this impression compared to physicians and medical assistants ($p<0.05$) (Table II). On the contrary, only 59.1% felt that the use of PPE will protect patients from contracting COVID-19. 46.6% of the respondents regarded PPE use as cumbersome, with 37.3% believed that it interferes with the care of patients with COVID-19. Significantly more physicians perceived PPE use as an impediment to providing care to patients ($p<0.001$). A great majority of 98.4% were confident that they understood the risk of COVID-19 to the patients and HCWs. Of the HCWs surveyed in this study, 93.8% felt that they could improve the compliance with the recommended PPE. A significantly higher extent of negative attitude was found among physicians than non-physicians towards PPE.

Behaviour and Organisational Factors

While 73.6% of the respondents exposed that their colleagues frequently failed to use the recommended PPE, 79.8% admitted to forgetting to change PPE between patients. Significant difference in the aforementioned behaviours was seen across the three different professional groups with the former $p<0.001$ and the latter $p<0.01$. In both behavioural aspects, physicians held the most negative behaviour towards PPE. In addition, 93.3% noted that they removed their PPE immediately after leaving the patients' room. Behaviour scores were generally poor and significantly associated with different professional roles.

Table I: Characteristics of the respondents

Category	n (%)	Mean (SD)
Age		30.57 (5.84)
20–29	108 (56.0)	
30–39	66 (34.2)	
40–49	19 (9.8)	
Gender		
Male	89 (46.1)	
Female	104 (53.9)	
Profession		
Physician	48 (25.7)	
Nurse	66 (34.2)	
Assistant medical officer	79 (40.9)	
Area of work		
ETD	131 (67.9)	
Infectious disease unit	23 (11.9)	
Others†	39 (20.2)	
Work with patients with COVID-19		
Yes	153 (79.3)	
No	40 (20.7)	

ETD (emergency and trauma department).
†Among the 39 other areas of work, 10 were intensive care unit staff, 12 were from the medical department, 10 personnel were from the orthopaedic department, 3 were otorhinolaryngology department staff, 1 each from the radiology and psychiatric departments, respectively and 2 were from step-down COVID centres.

Table II: Use of PPE during the COVID-19 pandemic: Knowledge, attitude and behaviour and organisational factors

	Physician (n = 48)	Nurse (n = 66)	Medical assistant (n = 79)	Total (n =1 93)
Knowledge				
• Correct recognition of PPE	70.8% (34)	75.8% (50)	73.4% (58)	73.6% (142)
• Proper use of protective eyewear and gown upon patient care	72.9% (35)	78.8% (52)	84.8% (67)	79.8% (154)
• Correct use of mask during patient care	77.1% (37)	80.3% (53)	82.3% (65)	80.3% (155)
• Proper understanding on hand hygiene***	79.2% (38)	31.8% (21)	24.1% (19)	40.4% (78)
Attitude				
• Use of PPE will protect HCWs from contracting COVID-19*	83.3% (40)	97.0% (64)	88.6% (70)	90.2% (174)
• Use of PPE will prevent patients from contracting COVID-19	59.3% (27)	54.5% (36)	64.6% (51)	59.1% (114)
• PPE use does not cause inconvenience	50.0% (24)	48.5% (32)	59.5% (47)	53.4% (103)
• Use of PPE does not interfere with patient care***	25.0% (12)	65.2% (43)	83.5% (66)	62.7% (121)
• I have the knowledge of COVID-19	97.9% (47)	95.5% (63)	98.7% (78)	97.4% (188)
• I am certain that I comprehend the risks of a pandemic for patients and HCWs	97.9% (47)	97.0% (64)	100% (79)	98.4% (190)
• I am sure that I can increase compliance with PPE	97.9% (47)	94.5% (63)	89.9% (71)	93.8% (181)
• High compliance (>80%) with PPE during patient care	89.6% (43)	77.2% (51)	73.4% (58)	78.8% (152)
Behaviour				
• My colleagues often failed to don PPE during patient care***	93.6% (45)	72.7% (48)	62.0% (49)	73.6% (142)
• I will doff my PPE straight after leaving the patient room	87.5% (42)	93.9% (62)	97.5% (77)	93.3% (181)
• I forget to switch PPE between patient upon patient care**	91.7%(44)	83.3% (55)	69.6% (55)	79.8% (154)
Organisation				
• PPE is easily accessible in the department	79.2% (38)	87.9% (58)	92.4% (73)	87.6% (169)
• I will be reprimanded by my supervisor	93.8% (45)	94.0% (62)	97.5% (77)	95.3% (184)
• I know when my patients are on COVID-19 precautions	91.7% (44)	89.4% (59)	86.1% (68)	88.6% (171)
Knowledge scores				
• Good knowledge	35.4% (17)	50.0%(33)	43% (34)	43.5% (84)
• Poor knowledge	64.6% (31)	50.0% (33)	57.0% (45)	56.5% (109)
Atitude scores**				
• Good attitude	33.3% (16	43.9% (37)	65.8% (52)	54.4% (105)
• Poor attitude	66.7% (32)	56.1% (29)	34.2% (27)	45.6% (88)
Behavior scores*				
• Good behavior	4.2% (2)	13.6% (9)	22.8% (18)	15.5% (29)
• Poor behavior	95.8% (46)	86.4% (57)	77.2% (61)	85.0% (164)

*p<0.05, **p<0.01, ***p< 0.001
p value achieved from Chi-square test

Table III: Relationship between knowledge and attitude of the use of PPE towards behaviour

	r value	*p* value
Knowledge	0.111	0.124
Attitude	0.313	0.000

$p < 0.05$

Table IV:Predictors of high compliance to PPE use among the healthcare workers

	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Age		
20–29	Ref.	
30–39	*2.55 (1.126, 5.714)	*2.150 (1.087, 4.253)
40–49	7.247 (0.927, 56.652)	
Gender		
Male	Ref.	
Female	1.146 (0.574, 2.285)	
Profession		
Physician	Ref.	
Nurse	0.395 (0.133, 1.176)	
Others	0.321 (0.112, 0.920)	
Area of work		
ETD	Ref.	
Infectious Disease	1.535 (0.486, 4.847)	
Others	2.198 (0.793, 6.095)	
Knowledge		
• Correct recognition of PPE	1.393 (0.656, 2.958)	
• Proper use of protective eyewear and gown during patient care	1.156 (0.578, 2.311)	
• Correct use of mask during patient care	1.984 (0.975, 4.038)	
• Proper understanding of hand hygiene	1.227 (0.602, 2.502)	
Attitude		
• I have knowledge of COVID-19	0.393 (0.063, 2.432)	
• Use of PPE will protect HCWs from contracting COVID-19	2.000 (0.702, 5.702)	
• Use of PPE will prevent patient from contracting COVID-19	0.981 (0.484, 1.990)	
• PPE use cause inconvenience during patient care	0.870 (0.434, 1.741)	
• Use of PPE interfere with patient care	**0.276 (0.450, 0.661)	0.395 (0.125, 1.242)
• I am sure that I can increase compliance toward PPE use	0.923 (0.188, 4.524)	
Behavior		
• My colleague forget to don PPE during patient care	***0.234 (0.113, 0.487)	*0.281 (0.133, 0.595)
• I will doff PPE straight after leaving the patient room	0.320 (0.040, 2.557)	
• I failed to switch PPE between patient upon patient care	**0.325 (0.150, 0.702)	0.758 (0.253, 2.272)
Organisational factors		
• PPE is easily attained in the department	0.492 (0.139, 1.740)	
• I will be reprimanded by my supervisor if I fail to adhere to PPE protocol	1.921 (0.459, 8.037)	
• I am aware of patients who are on COVID-19 precautions	1.181 (0.405, 3.439)	

*$p < 0.05$, **$p < 0.005$, ***$p < 0.001$

Out of the 193 respondents, 87.6% agreed that the recommended PPE was readily available in their department (Table II), 95.3% perceived some form of disciplinary action from their superiors in the event of compromised PPE practice, and 88.6% were aware that their patient was on COVID-19 precautions.

Attitude on the use of PPE showed statistically significant, moderate positive correlation with behaviour (Pearson correlation coefficient, r=0.313; $p<0.001$), whereas knowledge level did not influence behaviour (Table III).

Predictors of PPE Usage Compliance

High compliance (>80%) towards the use of PPE was proclaimed by 78.8% of respondents (Table II). Age group 30–39 years is a significant positive predictor to high compliance to PPE, whilst having the perception that PPE use interferes with patient care and behavioural factors such as failure to change PPE and reports of colleague forgetting to wear PPE were found to be significant negative predictors to high compliance with PPE protocol in univariate logistic regression (Table IV).

Age and reports of fellow colleagues neglecting PPE use during patient care were significant predictors of PPE compliance in both simple and multivariate logistic regression model analyses (Table IV).

DISCUSSION

The influenza A (H1N1) pandemic (2009), Severe Acute Respiratory Syndrome (SARS) outbreak (2002 and 2003) and the Middle East Respiratory Syndrome outbreak (2012) have highlighted HCW vulnerability to workplace infection.[16] PPE protects against contamination by acting as a physical barrier between pathogens and personnel.[17] In 2020, Lockhart et al.[18] suggested the combination of modified PPE comprising a N95 respirator, eye protection (surgical mask

with visor), disposable surgical gown, double high-cuffed (surgical-type) gloves, surgical hood with ties (head and neck covering) and knee-high shoe covering for aerosol-generating procedures, which aligns with the WHO guidelines, sans the doublegloving.[11,18] A proper selection of PPE and correct practice and competency in donning and doffing is essential to protect HCWs from COVID-19 and to prevent further transmission of the disease.[19,20]

According to the Centres of Disease Control and Prevention (CDC), hand hygiene must be performed for extra protection to potentiate the effectiveness of PPE. It is recommended to perform the hand hygiene steps immediately after the removal of all PPE as the hands might be contaminated upon doffing.[21] We found a remarkable lack of proper understanding on hand hygiene among subjects (40.4%), with significant variability between the three professional groups. The considerably poorer hand hygiene knowledge among nurses and medical assistants implies that special attention to infection prevention in this group is required.

Most respondents were confident that using PPE ensures protection from COVID-19 exposure. Ironically, only 59.1% believed that wearing PPE will prevent patients from contracting COVID-19, contrary to what would be expected from the former belief. This conflicting finding corresponds with a survey conducted during the H1N1 influenza pandemic by Hu et al.[22] The counterintuitive perceptions of the role of PPE illustrate that some HCWs are unaware that they are inadvertently protecting themselves and the patients by wearing PPE. The particular emphasis on the importance of PPE in protecting HCWs from COVID-19 may have sidetracked the other functions of PPE that are equally paramount in preventing hospital-acquired infection.[23] Nevertheless, further research is required to explore this finding.

Interestingly, 46.6% confessed that wearing PPE during patient care is inconvenient. A corresponding 37.3% of respondents agreed that using PPE interferes with patient care, with significant differences in beliefs across professional groups. A complete set of PPEs routinely worn for protracted periods during the care of patients with COVID-19 may cause a multitude of problems. Increased breathing resistance and humidity from N95 masks, vision restrictions from face shields, ineffective communication from muffled speech, thermal stress from layers of impermeable PPE and impaired manual dexterity and tactile sensation (especially with layers of gloves) are physiological stressors that potentially reduce compliance and impair a clinician's performance. This may eventually result in mental fatigue and psychological stress.[24,25] This perceived inconvenience is a contributing factor to the poor adherence to PPE.[22,26] While technological advancement in the construct of PPE remains far from optimal, several counter-measure strategies to address the problems arising from PPE use can improve the ability to provide quality care to patients. These strategies include regular training, careful planning of critically demanding duties, adequate rest and nutrition, breathing exercises, facilitating visual awareness, effective communication skills, lowering the threshold for additional assistance, appropriate temperature adaptation, the introduction of mindfulness training programs[25] and the provision of vigorous psychological support.[27,28]

We discovered a positive correlation between attitude and behaviour indicating HCWs with positive attitude and showed positive behaviour. Nevertheless, the level of knowledge did not translate to good PPE practice. Generally, respondents with good knowledge have higher odds of reporting high compliance. Contrariwise, HCWs with poor attitude and behaviour scores are less likely to self-report high compliance. Similar studies or studies akin to this research with PPE practice as one of the subcomponents appraised have revealed diverse outcomes with some studies showing knowledge correlates with good attitude and practice and the other studies showing the opposite findings.[14,22,29-33] The diverse study outcome is possibly due to multiple factors including the variation in participant demographics, study designs, data collection tools, research settings, institutions and regions. This may complicate the accurate comparison between knowledge, attitude, behaviour and compliance across these studies.

In our study, organisational factors, such as easy access to PPE has no significant association with high compliance to PPE although the majority agreed that PPE readily available. Conversely, Hu et al. and Daugherty et al. found a significant association between the availability of PPE and the level of compliance, affirming the importance of institutional-level interventions. Our survey showed that if respondents carried the perception of professional consequences from non-compliance to PPE protocol and awareness of patients under COVID-19 precautions, they were at higher odds to report high compliance. Compliance towards the usage of proper PPE could be enhanced with a concerted effort from all departments in the implementation of improved guidelines. This involves a dedicated team of safety managers created to monitor and enforce PPE adherence. This working party will also oversee the process of coaching and instilling safe PPE practice by coordinating regular workshops on the updated PPE recommendations, periodic simulated drills, and on-site trainings, as well as refresher courses to reinforce the proper practice of PPE. In addition, the incorporation of mindfulness-based cognitive training programs to improve resilience and manage burnout among HCWs should be considered.[34] A multiprong approach of regular and mandatory infection prevention and control training programmes for HCWs[3,35], and the enforcement of PPE protocol adherence by a regulatory team has resulted in significantly more competent PPE practice among HCWs.[30]

We discovered that a negative attitude (notion of PPE use interferes with patients' care) and recusant behaviour, such as the failure to don PPE during patient care and the failure to switch PPE between patients, were significant independent factors of low compliance towards PPE wear in the univariate analysis. The perceived obstruction in patient care was reported in previous studies by Daugherty, Hu and Seitz.[14,22,29] Failure to switch PPE might be challenging owing to time constraints and alarge number of patients with the COVID-19 pandemic, as additional time and effort is required to ensure this is performed correctly before entering a patient's room (and subsequently removed meticulously in an appropriate sequence to prevent self-contamination).[14,21,22]

LIMITATIONS

This study is a voluntary survey with feedback reflecting on the opinions and perceptions of the respondents instead of the actual situation. As this study relied on a self-reported questionnaire, there is an inclination to overrate favourable attitudes and behaviours. A comprehensive instrument validation and reliability assessment would have increased the virtue of the tool. The sample size of the study may be under-representing the actual number of HCWs in Malaysia. Therefore, an extension of the study to include university hospitals, district hospitals and hospital laboratories would be ideal to provide a more comprehensive picture. Finally, language may have been a barrier to several HCWs as the survey was only offered in English.

CONCLUSION

HCWs in Malaysia have suboptimal knowledge levels of hand hygiene. There was a significant positive correlation between attitude and the behaviour of HCWs. Age and negative behaviour towards PPE use have been recognised as predictors of compliance towards PPE use. Our study highlights the necessity to analyse discrepancies in PPE practice and the contributing elements to the disparities among HCWs. Understanding the perceptions and obstacles of PPE use provides an insight into the factors that may influence compliance with PPE during the pandemic. Furthermore, the imperative exploration of PPE practice among HCWs would assist in the development of a more comprehensive control and preventative strategy as part of health emergency preparedness and response to possible infectious threats in the future.

ETHICAL APPROVAL

This study received approval from the ethics committee of Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-20-878-54908 [IIR]).

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CONFLICT OF INTEREST

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Dementia detection practice among primary care practitioners: A cross-sectional study in Hulu Langat District, Selangor

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ABSTRACT

Introduction: Dementia is a global challenge for healthcare systems, including Malaysia. Despite evidence-based Clinical Practice Guidelines (CPG) for dementia management in primary care, detection is poor. Improving detection rates requires understanding current practice and influencing factors. This study aims to assess the practice of cognitive evaluation among primary care practitioners (PCPs) and its associated factors, as well as its correlation with their knowledge and attitudes towards early dementia diagnosis.

Materials and Methods: A cross-sectional study conducted online, using Google Form™ recruited 207 Medical Officers from 14 public primary health centres, with a response rate of 74%. The Knowledge, Attitude and Practice Questionnaire for Family Physicians (KAPQFP) was used to assess PCPs' knowledge, attitude and practice in dementia care. Items in each domain were scored on a 4-point Likert scale, with scores ranging from 1 to 4. Each domain's mean score was divided by 4 and converted to a scale of 100, with higher scores indicating better knowledge, attitude and practice. Bivariate analyses were conducted to determine the factors associated with cognitive evaluation practice.

Results: The overall mean practice score was 3.53±0.52 (88.3%), which is substantially higher than the mean score for perceived competency and knowledge of 2.46±0.51 (61.5%). The mean score for attitude towards dementia and collaboration with nurses and other healthcare professionals was 3.36±0.49 (84.0%) and 3.43±0.71 (85.8%), respectively. PCPs with prior dementia training showed better practice (p=0.006), as did PCPs with longer primary care work experience (p=0.038). A significant positive association was found between knowledge-practice ((r_S=0.207, p=0.003), attitude towards dementia practice ((r_S=0.478, p<0.001), and attitude towards collaboration with other healthcare professionals-practice (r_S= 0.427, p<0.001). Limited time and inadequate knowledge regarding dementia diagnosis and cognitive evaluation tools were among the reasons cognitive evaluations were not performed.

Conclusion: PCPs demonstrated better practice of cognitive evaluation, as compared to their knowledge and attitude. Given that their perceived competency and knowledge on dementia diagnosis is low and is positively associated with their practice, it is crucial to implement a comprehensive dementia training to enhance their knowledge and confidence on early detection of cognitive decline and cognitive evaluation in order to achieve better dementia detection in primary care.

KEYWORDS:
dementia, primary care practitioners, knowledge, attitude, cognitive evaluation practice

INTRODUCTION

Dementia is a syndrome characterised by gradual and progressive decline in cognitive functions beyond what would be expected from natural ageing, making it one of the major causes of disability and dependence worldwide. It is currently the seventh leading cause of death globally with 10 million new cases diagnosed annually.[1] Malaysia reported an 8.5% prevalence of dementia,[2] close to the 10.7% estimated prevalence of Alzheimer's disease in the United States.[3] Given the world's ageing population, local prevalence of dementia is predicted to rise.[4]

Persons living with dementia (PLWD) and their caregivers experience various emotional, physical, financial and social consequences. As dementia progresses, caregivers' quality of life declines considerably.[5,6] Early dementia detection and diagnosis allow PLWD to receive evidence-based treatment and care plans for a better disease outcome and caregivers to receive early access to counseling and support services.[7] The WHO global action plan proposes timely dementia diagnosis and integrating dementia treatment and care into primary care as part of the long-term dementia care system.[8] Nevertheless, dementia remains under-detected in the community.[9,10] Dementia under-detection is a worldwide problem; even in high-income nations with advanced medical technologies, only 20–50% of dementia cases are recorded in primary care.[11]

Prior studies revealed that dementia detection by PCPs is hindered by their inability to recognise early dementia symptoms, limited knowledge, skills and confidence in

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dementia diagnosis, as well as negative perception and attitude towards early dementia diagnosis.[12-15] These barriers make PCPs hesitant to perform cognitive testing, hence many people with cognitive impairment go undiagnosed.[16] Evaluation of cognitive function is necessary if the patient or family members report memory problems or the PCPs suspect cognitive impairment. As the first point of contact for most older adults in the community, PCPs should be competent in cognitive decline detection, cognitive testing, and dementia diagnosis. Most studies have focused on PCP's knowledge, attitudes, and confidence towards dementia diagnosis.[17-21] However, limited studies explored PCPs' cognitive evaluation practice. Understanding the current practice and its influencing factors is critical to enhance detection and improve primary healthcare system. This study aims to assess the cognitive evaluation practice among PCPs and its associated factors, as well as its correlation with their knowledge and attitudes towards early dementia diagnosis. This study will also explore the reasons for not performing cognitive evaluation. Malaysia lags behind its ASEAN neighbours in having a National Dementia Strategy in which timely diagnosis of dementia is a priority. This information can assist the public health representative in developing an improvement strategy focusing on overcoming the issues related to the dementia under-detection in primary care. Data from this study can be used as a baseline value for future large-scale research to support and expedite a National Dementia Strategy.

MATERIALS AND METHODS

Study *Sampling*

This cross-sectional study recruited PCPs from 14 public primary healthcare clinics in Hulu Langat district, Selangor from July to September 2022. The inclusion criteria were registered PCPs who manage adult patients aged 60 and above. Those who refused consent were excluded from this study. Universal sampling was used for data collection. The sample size was calculated using a single mean formula based on the mean score of general practitioners' attitudes towards dementia from a prior study conducted in China (22). A minimum sample of 195 participants was needed to reach a precision of 0.05 with a 95% confidence level, with an additional 40% to account for possible non-respondents.

Data Collection

A self-administered online *Google Forms™* questionnaire was used for data collection. First, Medical Officer-in-Charge (MOIC) at each of the 14 public primary healthcare clinics received the questionnaire link. They distributed the link to the PCPs via their respective clinic's group chat. The study's information and purpose were explained in the *Google Forms™* and informed consent was obtained before PCPs proceeded with the questionnaire. Only completed questionnaires can be submitted to minimise data analysis errors. Three reminders were sent, one every 2 weeks, after which no response was considered a non-responder.

Study Instrument

This study used the Knowledge, Attitude and Practice Questionnaire for Family Physicians (KAPQFP) by Genevieve Arsenault-Lapierre.[23] This questionnaire explored the elements of dementia detection, diagnosis and treatment based on the three domains, the PCP's knowledge, attitude and practice (KAP). It is a validated questionnaire with the internal consistency (Cronbach's alpha) of the items within each factor ranged from 0.66 to 0.91. The knowledge domain consisted of 11 items that evaluated the perceived competency and knowledge in dementia diagnosis and care plan. The attitude domain is divided into two parts, with six items assessing the attitude towards dementia care and three items assessing the attitude towards collaboration with nurses and other healthcare professionals. There were seven items in the practice domain that looked at the practice of cognitive evaluation. The questionnaire was adapted to the local healthcare setting for the purpose of this study, i.e., the practice component of the questionnaire was updated to include seven additional questions, while one question in the knowledge section was adapted to the Malaysian setting by replacing the Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD) guideline[24] with Malaysian Clinical Practice Guideline (CPG)on Management of Dementia, Third Edition.[25] The additional items assessed the self-reported burden of dementia patients in public primary care practice, choice of cognitive assessment tools used, reasons for not performing cognitive assessment and specialist referral for patients with suspected dementia. These questions had been locally validated by two-panel experts and analysed descriptively, without affecting the questionnaire's scoring. The final questionnaire consisted of 44 items divided into two sections: socio-demographic and knowledge, attitude and practice (KAP).

Scoring for Knowledge, Attitude and Practice Domains

Each item was evaluated using 4-point Likert scale. Participants indicate their level of agreement with each item as follows: 1=Disagree, 2=Somewhat disagree, 3=Somewhat agree, 4=Agree. Reverse coding was used for negative statements. Each item has a minimum score of 1 and a maximum score of 4. The responses "Don't know" and "Not applicable" were excluded from scoring and data analysis. Domain scores were calculated by taking the mean score of each item within the domain. By dividing the mean by a maximum total of 4, these domain scores were converted to a scale of 100. The higher the score, the better the participants' knowledge, attitude and practice.

Statistical Analysis

All data were analysed using The Statistical Package for Social Science (SPSS) version 28.0. Variables in the study were participants' socio-demography, clinical experience, knowledge, attitude and practice. The cognitive evaluation practice score was used as a study outcome indicator. Data were descriptively presented in frequency (n), percentage (%), mean value with standard deviation (SD) and median value with interquartile range (IQR). The normality test revealed that the outcome variable, the practice score, was not normally distributed. Hence, non-parametric analyses were used to further analyse the data. Mann–Whitney*U* and Kruskal–Wallis tests were used to compare practice scores across independent variables, and Spearman's correlation coefficient was used to assess the strength of association between scores. The significance level was set at p value < 0.05 (2-sided).

Table I: Characteristics and demographics of study participants (n = 201)

Variables	n (%)
Age (years)	
Median (IQR)	35.0 (4.0)
Gender	
Male	20 (10.0)
Female	181 (90.0)
Ethnicity	
Malay	163 (81.1)
Indian	23 (11.4)
Chinese	13 (6.5)
Bumiputra Sabah/Sarawak	2 (1.0)
Postgraduate qualification in family medicine	
Without postgraduate qualification	173 (86.0)
With postgraduate qualification	28 (14.0)
Duration of practice in primary care (years)	
Median (IQR)	6.0 (6.0)
Clinical experience in geriatric subspecialty	
No	182 (90.5)
Yes	19 (9.5)
Experience with dementia care	
No	144 (71.6)
Yes	57 (28.4)
Dementia training	
No	155 (77.1)
Yes	46 (22.9)

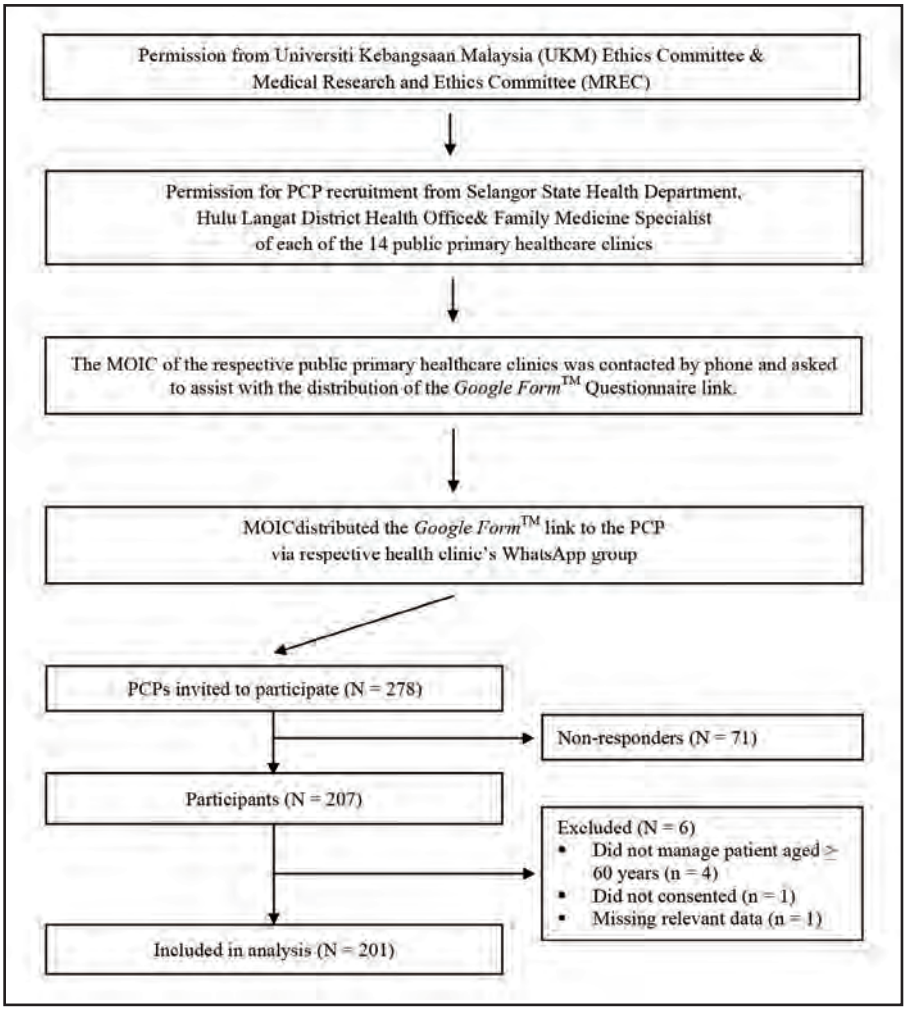

Fig. 1: Study flow chart

Table II: Participants' answers on knowledge, attitude and practice questions

Item	Likert scale[a], n (%)				Median (IQR)
	Disagree	Somewhat disagree	Somewhat agree	Agree	
Perceived competency and knowledge in dementia care					
I believe that I have the skills to:					
1) Diagnose dementia.	7 (3.5)	49 (24.4)	93 (46.3)	45 (22.4)	3.0 (1.0)
2) Develop an appropriate care plan for patients with dementia.	16 (8.0)	75 (37.3)	76 (37.8)	24 (11.9)	3.0 (1.0)
3) Educate patients and their families about dementia.	10 (5.0)	48 (23.9)	94 (46.8)	42 (20.9)	3.0 (1.0)
4) Inform patients and family of the diagnosis.	13 (6.5)	47 (23.4)	82 (40.8)	51 (25.4)	3.0 (2.0)
5) I nvolve the caregiver in the diagnosis.	7 (3.5)	33 (16.4)	99 (49.3)	53 (26.4)	3.0 (1.0)
In my day-to-day work:					
1) I know the diagnostic criteria for dementia.	18 (9.0)	57 (28.4)	65 (32.3)	52 (25.9)	3.0 (2.0)
2) I regularly keep up to date on the Malaysian Clinical Practice Guideline (CPG) on Management of Dementia, 2021.	28 (13.9)	64 (31.8)	66 (32.8)	32 (15.9)	2.0 (1.0)
3) I feel comfortable prescribing dementia medications.	70 (34.8)	76 (37.8)	33 (16.4)	12 (6.0)	2.0 (1.0)
4) I refer my patients to a specialist for diagnosing dementia.[b]	9 (4.5)	22 (10.9)	69 (34.3)	101 (50.2)	2.0 (1.0)
5) I refer my patients to a specialist for managing cases of dementia.[b]	4 (2.0)	22 (10.9)	66 (32.8)	109 (54.2)	2.0 (1.0)
6) I think that dementia diagnoses are best left to specialist.[b]	35 (17.4)	56 (27.9)	51 (25.4)	52 (25.9)	2.0 (2.0)
Attitude towards dementia and interprofessional collaboration					
I think that:					
1) Several things can be done to improve the quality of life of a patient with dementia	3 (1.5)	4 (2.0)	60 (29.9)	131 (65.2)	4.0 (1.0)
2) Several things can be done to improve the quality of life of caregivers.	1 (0.5)	6 (3.0)	59 (29.4)	131 (65.2)	4.0 (1.0)
3) An early diagnosis of dementia usually does more harm than good.b	99 (49.3)	40 (19.9)	28 (13.9)	29 (14.4)	4.0 (2.0)
4) The families of patients with dementia prefer knowing the diagnosis as soon as possible.	5 (2.5)	18 (9.0)	72 (35.8)	96 (47.8)	4.0 (1.0)
5) Until we have an effective treatment, diagnosing dementia is not a priority.[b]	79 (39.3)	65 (32.3)	31 (15.4)	23 (11.4)	3.0 (2.0)
6) In presence of symptoms, early diagnosis of dementia is important.	3 (1.5)	7 (3.5)	67 (33.3)	116 (57.7)	4.0 (1.0)
I think that my collaboration with:					
1) The nurse or allied health collaborators in my team is essential to diagnose dementia.	9 (4.5)	15 (7.5)	72 (35.8)	100 (49.8)	4.0 (1.0)
2) The nurse or other allied professionals in my team is essential to develop care plans for patients with dementia.	6 (3.0)	10 (5.0)	66 (32.8)	113 (56.2)	4.0 (1.0)
3) The nurse or allied health collaborators in my team is essential for the management of cases of dementia.	5 (2.5)	11 (5.5)	68 (33.8)	112 (55.7)	4.0 (1.0)
Practice of cognitive evaluation					
I look for the presence of cognitive impairment in my patients when:					
1) They seem to have a short memory.	1 (0.5)	4 (2.0)	61 (30.3)	132 (65.7)	4.0 (1.0)
2) They lose or misplace things.	3 (1.5)	9 (4.5)	62 (30.8)	125 (62.2)	4.0 (1.0)
3) They complain about memory problem.	4 (2.0)	8 (4.0)	50 (24.9)	139 (69.2)	4.0 (1.0)
4) Family members believe that they may have dementia.	2 (1.0)	10 (5.0)	59 (29.4)	127 (63.2)	4.0 (1.0)
5) They mix up their medications.	2 (1.0)	27 (13.4)	75 (37.3)	93 (46.3)	3.0 (1.0)
6) They repeat themselves.	4 (2.0)	17 (8.5)	71 (35.3)	106 (52.7)	4.0 (1.0)
7) Family members report changes in behaviors.	0	6 (3.0)	55 (27.4)	137 (68.2)	4.0 (1.0)

*"Don't know" and "Not applicable" responses were disregarded for scoring.
[a] Likert scale from 1 (Disagree) to 4 (Agree).
[b]Negative statement

Table III: Inferential relationship between practice scores and its' influencing factors (sociodemography, clinical experience, knowledge

Variables	Median	IQR	Mean rank	Statistical test	*p* value
Age				0.120[c]	0.088
Gender				0.927[a]	0.354
Male	3.64	0.96	89.83		
Female	3.71	0.93	102.23		
Ethnicity				5.33b	0.070
Malay	3.71	0.71			
Indian	3.00	0.86			
Chinese	3.71	0.86			
Bumiputera Sabah/Sarawak	4.00	0.00			
Postgraduate qualification in Family Medicine				0.893a	0.372
Without postgraduate qualification	3.71	1.00	99.56		
With postgraduate qualification	3.86	0.71	109.89		
Duration of practice in primary care				**0.147c**	**0.038***
Clinical experience in geriatric subspecialty				-0.915a	0.360
Yes	3.71	1.71	89.66		
No	3.71	0.86	102.18		
Experience with dementia care				-0.175[a]	0.861
Yes	3.71	1.00	99.89		
No	3.71	0.86	101.44		
Dementia training				**2.756[a]**	**0.006***
Yes	3.86	0.46	121.28		
No	3.71	1.00	94.98		
Perceived competency and knowledge in dementia care				**0.207[c]**	**0.003***
Attitudes towards dementia				**0.478[c]**	**<0.001***
Attitudes towards collaboration with nurses and other health care professionals				**0.427[c]**	**<0.001***

[a]Mann–Whitney U test and Z value
[b]Kruskal–Wallis test and H value
[c]Spearman correlation test and rho value
*Significant at p <0.05

Table IV: PCPs' practice of cognitive evaluation and specialist referral

Item	Frequency (n)	Percentage (%)
Cognitive evaluation tools used by participants (n = 168).[a]		
Mini Mental State Examination (MMSE)	159	94.6
Mini-Cog	29	17.1
Montreal Cognitive Assessment (MoCA)	22	13.1
Reason for not performing cognitive assessment (n = 33).[a]		
Lack of time to assess the patient	24	72.7
Did not know how to manage a patient with dementia	12	36.4
Did not know what tool to use for cognitive assessment	8	24.2
Physical health problem is more important to manage than cognitive problem	1	3.0
Patient referred to specialist clinic	1	3.0
Specialist referral (n = 164).[a]		
Psychiatrist	86	52.4
Geriatrician	66	40.2
Neurologist	26	15.9
General physician	16	9.8
Geriatric psychiatrist	11	6.7
Family medicine specialist	2	1.2
Psychologist	1	0.6
Memory clinic	1	0.6
Reason for not referring to specialist (n = 37).[a]		
Unsure diagnosis	15	40.5
Did not know where to refer the patient	8	21.6
Lack of time to prepare for the referral	4	10.8
Patient refusal	2	5.4
Patient already under follow-up	2	5.4
Lack of time for proper assessment	1	2.7

[a]Participants were allowed multiple choices.

RESULTS

Characteristics and Socio-demographic Information

The overall response rate was 74% and 201 out of the 278 PCPs approached completed the questionnaire. The participants' median age was 35.0 (IQR 4.0) years. The median duration of primary care practice was 6.0 (IQR 6.0) years. Results showed that only 14% of participants held postgraduate qualifications in family medicine (FM). Table I summarises the population's detailed characteristics.

Knowledge, Attitude and Practice Mean Scores

The mean score for practice of cognitive evaluation was 3.53±0.52 (88.3%), which was substantially higher than the mean score for perceived competency and knowledge in dementia care of 2.46±0.51 (61.5%). The majority of participants exhibited a positive attitude towards dementia and collaborations with nurses and other health care professionals, with overall mean scores of 3.36±0.49 (84.0%) and 3.43±0.71 (85.8%), respectively.

Perceived Competency and Knowledge in Dementia Care

Table II shows that the items with low scores are those concerning dementia diagnosis and management and whether PCPs stay current on Malaysian Clinical Practice Guideline (CPG) on Management of Dementia with median score 2.0 (IQR 1.0) out of 4.0. Most participants performed poorly in negative statement items in which they prefer referring their patients to specialists for diagnosis and management, and they believe dementia diagnosis is best left to specialists. There was a moderate score for items pertaining to perceived competence in dementia diagnosis with median score 3.0 (IQR 1.0) and family liaison with regards to delivering diagnosis and dementia education with a median score of 3.0 (IQR 2.0) and 3.0 (IQR 1.0), respectively.

Attitude Towards Dementia and Collaboration with Nurses and Other Healthcare Professionals

With respect to attitude towards dementia, majority of participants showed a positive attitude with more than 80% of them disagreed with the negative statement that early dementia diagnosis usually does more harm than good with a median score 4.0 (IQR 2.0) out of 4.0 (Table II). However, over a quarter of participants thought that dementia diagnosis is not a priority until an effective treatment is available, giving a lower median score of 3.0 (IQR 2.0). On the other hand, more than 85% of PCPs agreed that collaboration with nurses and other health care professionals is essential for diagnosing and managing dementia cases with a median score 4.0 (IQR 1.0).

Practice of Cognitive Evaluation

Table II shows that the majority of participants would do a cognitive evaluation on patients who come with symptoms or signs of cognitive impairment, giving the median score of 4.0 (IQR 1.0). However, 14.4% of participants disagreed that they look for cognitive impairment when patients mix up their medications, giving a lower median score of 3.0 (IQR 1.0).10.5% of participants were less likely to perform cognitive evaluation on patients who repeat themselves.

Relationship Between Practice Score and PCPs' Socio-demography, Clinical Experience, Knowledge and Attitude

Table III represents bivariate analysis of participants' practice score across their socio-demography, clinical experience, knowledge and attitude. The practice score was statistically significantly higher among participants with a longer duration of practice in primary care setting (p=0.038). Participants who had dementia training had higher practice score than those who did not (median score 3.86 vs 3.71, p=0.006). There was a statistically significant positive correlation between knowledge-practice (r_s=0.207, p=0.003), attitudes towards dementia practice (r_s = 0.478, p<0.001) and attitudes towards collaboration with nurses and other health care professionals-practice (r_s=0.427, p< 0.001).

DISCUSSION

In recent years, several countries have recognised the burden of dementia and the challenge of dementia under diagnosis. Some countries have successfully developed dementia strategies and clinical practice guidelines for primary care dementia detection. Malaysia lags behind its ASEAN neighbours in having a National Dementia Strategy in which timely dementia diagnosis is a priority. This study was conducted with the understanding that PCPs are patients' first point of contact, and with the burden of non-communicable disease (NCD), PCPs should be able to understand how dementia will further affect NCD management. Therefore, dementia under-detection in primary care must be addressed.

Practice of Cognitive Evaluation and Specialist Referral

PCPs mean practice score was comparable to their attitude, but however significantly higher than their perceived competency and knowledge in dementia diagnosis and care. There were 14.4% of the PCPs who were less likely to perform cognitive evaluation on patients who mixed up their medications. We postulate that they may not recognise medication confusion as a symptom of cognitive decline and consider other factors that contribute to it, such as polypharmacy and patients' insufficient knowledge regarding their illnesses and prescribed medications.[26]

Similarly, 10.5% of the PCPs were less likely to perform cognitive evaluation on patients who repeat themselves. Our assumption is that they may have mistakenly believed that repetitive speech is a normal part of ageing and nothing can be done.[27] Knowledge in dementia diagnosis is still lacking among the PCPs, which may affect their practice. Measures should be taken to improve PCPs' knowledge on cognitive decline in order to enhance cognitive evaluation and improve dementia detection in primary care.

PCPs reported time as the most common reason for not performing cognitive evaluation, which is consistent with the findings of Raphael et al. interpretive scope review.[15] Multidisciplinary team involvement may address this issue by assigning a trained staff to perform cognitive evaluation beforehand to reduce PCPs' consultation time. This may require prior structured training and education to ensure that each team member understands their role and responsibilities. Some PCPs in the current study did not assess

cognitive function because they believed physical health was more important. In a systematic review by Aminzadeh and colleagues, several PCPs believed that early diagnosis has minimal therapeutic benefit, and that dementia stigma may have detrimental impact, hence prioritizing physical health over dementia symptoms.[13] Additionally, PCPs also reported that the main barriers to performing cognitive evaluation and referring patients to specialists were uncertainty about the diagnosis and a lack of knowledge regarding dementia management and cognitive evaluation tools. Effective measures are required to tackle the gaps in the PCPs' attitude, knowledge and skills in an effort to acknowledge these issues. While CPG can be a useful tool, nearly half of the PCPs in current study were unaware of the guidelines and may not keep up with its recommendations. Primary care-focused education in the form of academic detailing may provide more contextualised dementia training, which can encourage the implementation of guidelines besides having a positive impact on PCPs' knowledge, confidence and skills.28

Association Between PCPs' Clinical Experience and Practice of Cognitive Evaluation

PCPs with prior dementia training are shown to have a better practice of cognitive evaluation. Consistent with this finding, a study by Lathren et al., had demonstrated that dementia training program markedly improved PCPs' clinical dementia skills and significantly increased the use of cognitive evaluation tools.[29] Dementia training can provide PCPs with the necessary knowledge regarding cognitive impairment and the importance of early dementia diagnosis. Training on the use of cognitive evaluation tools may increase their confidence in their diagnostic skills which could reduce their hesitancy on performing cognitive evaluation. This study also discovered that PCPs with longer work experience in primary care had better cognitive evaluation practice. This tendency may be explained by the fact that when PCPs work longer in primary care, they encounter more elderly patients, which increases their ability to notice cognitive decline in their patients. A practical education intervention may provide them with a better guidance to improve their ability for early dementia detection.[30]

Association Between PCPs' Perceived Competency and Knowledge in Dementia Diagnosis and Practice of Cognitive Evaluation

PCPs in current study reported a higher cognitive evaluation practice score as compared to their perceived competency and knowledge in dementia diagnosis and care plan. Most PCPs believed they could diagnose dementia, involve caregivers, educate, and develop an appropriate care plan, but only less than one-third are confident with these skills. PCPs also demonstrated a lack of confidence in diagnosing and initiating dementia treatment. This could be due to the fact that PCPs in Malaysia not typically managing dementia patients at the primary care level, which is the actual local practice in Malaysia as recommended by the 2021 Malaysian CPG on dementia management, which recommends referring suspected dementia patients to a tertiary centre for further investigations and confirmatory diagnosis.[25] Similar to the conclusion made by Aminzadeh and colleagues in a systemic review, lack of experience in managing dementia patients may make PCPs feel less knowledgeable about the disease, which might reduce their level of competence and confidence in their ability to recognise and diagnose dementia.[13]

This study had demonstrated that perceived competency and knowledge in dementia diagnosis are positively associated with the practice of cognitive evaluation. Consistent with this finding, a study by Heim et al. revealed that lack of knowledge was the main obstacle to performing cognitive evaluations and that PCPs who participated in dementia education were more likely to perform such evaluations than those who did not. Since PCPs are the first point of contact with elderly patients, it is crucial that they are well-versed in necessary knowledge on cognitive decline and evaluation. Hence, educational programs should provide enough exposure to these areas to improve dementia detection in primary care setting.

Association between PCPs' Attitude towards Dementia and Practice of Cognitive Evaluation

PCPs in the Hulu Langat district have a positive attitude towards dementia, which is also positively associated with their cognitive evaluation practice. There are, however, not many studies that examine the relationship between these two factors. Nevertheless, a few studies have shown a positive association between PCPs' attitude towards dementia and their dementia care skills and management approach after dementia diagnosis.[19,22,31] Geriatric competencies and self-efficacy expectations have been shown to influence PCPs' attitude towards dementia diagnosis.[21] Measures to increase geriatric knowledge and competence among PCPs are essential and should serve as the basis to expedite a national dementia policy.

Association Between PCPs' Attitude towards Collaboration with Nurses and Other Healthcare Professionals and Practice of Cognitive Evaluation

PCPs in this study generally demonstrated positive attitude towards interprofessional collaboration, indicating a desire for shared care with nurses and other healthcare professionals in diagnosing and managing dementia. PCPs' attitude has also shown to be positively associated with their practice of cognitive evaluation. Shared care initiatives are best represented by PCPs, nurse practitioners, occupational therapists, pharmacists, social workers, and mental health counsellors, who may help with cognitive assessment to reduce PCPs' consultation time and provide long-term dementia care.[32-34] To succeed, a care pathway must be established so multidisciplinary team members can follow evidence-based clinical practice guidelines and best local practice recommendations and be appropriately guided on their roles and responsibilities. Prince et al. recommend that dementia care pathway should include a basic curriculum as well as in-service training on how to provide dementia care as a team.[35]

STRENGTH AND LIMITATIONS

To the best of our knowledge, this is the first study that assessed the practice of dementia detection among public PCPs in Hulu Langat District. Several limitations were identified. The PCPs' perceived competency and knowledge were scored based on KAPQFP questionnaire designed in

Canadian healthcare setting, to assess their abilities to diagnose and manage dementia in primary healthcare centres. In Malaysian healthcare, however, PCPs serve as gatekeepers to direct patients with suspected dementia to tertiary centres for confirmatory diagnosis and further management. To properly assess PCPs' dementia knowledge and competency, future research should utilise a study tool relevant to Malaysian practice. The survey method did not objectively assess the actual practice of PCPs. Participant observation study methods should be considered in future research to better evaluate the cognitive evaluation practice. Finally, the study sample was limited to public primary healthcare clinics in Hulu Langat district; thus, caution is suggested in generalizing the study findings.

A Malaysian National Dementia Strategy should be expedited to support the development of clinical care pathways between primary care and tertiary centres to improve shared care collaboration among multidisciplinary teams for better dementia detection and patient outcomes. Future research should evaluate the adherence of PCPs to dementia screening practices based on Malaysian CPG on dementia management. It would also be advisable to explore the collaboration of primary healthcare providers with other members of multidisciplinary teams in dementia care once the diagnosis is made, as this is the fundamental role of primary care in long-term dementia management in the community.

CONCLUSION

PCPs in the Hulu Langat District demonstrated better practice of cognitive evaluation, as compared to their knowledge and attitude, with longer primary care working experience and dementia training contribute to a better practice. While PCPs' perceived competency and knowledge of dementia diagnosis, as well as their attitude towards dementia and interprofessional collaboration, are positively associated with their practice, cognitive evaluation is hindered by inadequate knowledge regarding dementia diagnosis and cognitive evaluation tools. More training in these areas is required to increase PCPs' knowledge and confidence in identifying dementia symptoms and committing to cognitive evaluation. Our healthcare system differs from several other countries with established National Dementia Strategies, such as Canada, where healthcare providers may diagnose, treat, and manage dementia in primary care settings. On the other hand, in our setting, primary care is not well-equipped to diagnose and manage dementia due to a lack of resources where further investigations and medications for dementia are only available in tertiary centres. Hence, the strategy to strengthen dementia care in our country at the moment should focus on PCPs' training in enhancing their knowledge and competency in early detection of cognitive decline and cognitive evaluation. We should also aim to upgrade the facilities and support in primary care in the future to cope with the increasing disease burden.

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ETHICAL APPROVAL

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research.

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ORIGINAL ARTICLE

Prevention of mother-to-child transmission (MTCT) of hepatitis B virus: An observation of routine practice in a tertiary liver centre before and after the introduction of the Global Health Sector Strategy on Viral Hepatitis (GHSSVH)

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ABSTRACT

Introduction: Worldwide, around 296 million people have hepatitis B virus (HBV) infection, most commonly transmitted from mother-to-child. Global Health Sector Strategy on Viral Hepatitis (GHSSVH) was introduced in May 2016, calling for elimination of viral hepatitis by 2030. This study aims to compare practice in a tertiary liver centre before and after GHSSVH introduction for prevention of mother-to-child transmission (MTCT).

Materials and Methods: This retrospective cohort study was performed in a tertiary referral liver centre in Malaysia, using data from electronic medical record from January 2015 to December 2019. A total of 1457 medical records of female with HBV infection were screened. The inclusion criteria of the study were pregnant women with HBsAg positive or known to have HBV infection during the study period. We excluded patients with co-infections of other types of viral hepatitis or human immunodeficiency virus, concurrent liver diseases (e.g.: autoimmune hepatitis, Wilson's disease), previous organ transplant and malignancy—except for hepatocellular carcinoma (HCC).

Results: This study included 117 pregnancies and 21/117 (17.9%) were on antiviral therapy (AVT) for HBV. In 2017–2019, 13/18 (72.2%) of those with HBV DNA >200,000IU/ml were on AVT, compared to 5/9 (55.6%) for 2015–2016, indicating 58% (95% CI −63% to 568%) higher odds of being on AVT in post GHSSVH group after accounting for HBV DNA.

Conclusion: Uptake of maternal AVT for the prevention of MTCT shows an increased trend since the introduction of GHSSVH, with room for improvement.

KEYWORDS:
Antiviral therapy, Global Health Sector Strategy on Viral Hepatitis (GHSSVH), hepatitis B virus, mother-to-child transmission, neonatal immunoprophylaxis failure, prevention

INTRODUCTION

Worldwide, it is estimated that there are around 296 million people living with chronic hepatitis B infection. Malaysia is one of the countries in World Health Organisation (WHO) Western Pacific Region, which has the highest burden of infection, where 116 million people are infected.[1] It is a major global health problem as approximately 15–40% of patients with hepatitis B virus (HBV) infection may develop complications like liver cirrhosis, hepatocellular carcinoma or liver failure.[2] As such, WHO aims to eliminate viral hepatitis by 2030.

Each year, there are about 1.5 million new hepatitis B infections, most commonly transmitted from mother to child in highly endemic areas like Malaysia. Unlike infection acquired in adulthood, which leads to chronic infection in less than 5% of cases, infection acquired in infancy and early childhood resulted in chronic hepatitis in about 95% of cases,[1] which is the main contributor to the morbidity and mortality related to HBV infection.[3] Therefore, efforts should be focused on the prevention of new hepatitis B infection among the infants by prevention of mother-to-child transmission (MTCT) with various strategies.[4]

Studies have shown that HBV transmission, despite adequate neonatal immunoprophylaxis, can still occur in highly viraemic mothers, with HBV DNA >6 $\log_{10}$ copies/ml,[5] prompting additional measures to further reduce this form of vertical transmission. Immunoprophylaxis with HBV vaccines and Hepatitis B Immunoglobulin (HBIG), which were developed in the 1980s, have been estimated to prevent approximately 90% of new infections among infants. Causes of immunoprophylaxis failure include intrauterine infection, which cannot be prevented by prophylaxis administered at birth, peripartum infection resulting from breakthrough infection that occurred at delivery and postnatal infection occurring in small proportion of children who failed to mount an adequate immune response to the immunoprophylaxis given.[6]

Despite the abundance of data available for hepatitis treatment and prevention, viral hepatitis as a public health threat remained neglected and made little progress compared to diseases like human immunodeficiency virus (HIV) or malaria. Lack of international investments in viral hepatitis programmes especially in low-income and middle-income countries, as well as the paucity of global guidance on

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strategies framework are the main hurdles in achieving hepatitis elimination.[7] Consequently, in 2016, the WHO Global Health Sector Strategy on Viral Hepatitis (GHSSVH) provided the initial guidance for the elimination of viral hepatitis as a public health problem by 2030.[8] It provides countries with a range of options for measurements of targets in assessing progress towards elimination, depending on available surveillance data and capacity. Gaps can then be identified and guide decisive actions towards achieving the goal.[8] Prevention of MTCT of HBV is among the core intervention areas documented in this guidance[9] whereby the use of perinatal antiviral therapy (AVT) when indicated is advocated.[10]

Closer to home in Malaysia, the targets set by National Strategic Plan for Hepatitis B and C 2019–2023 with regards to the prevention of MTCT of HBV only cover antenatal hepatitis B screening and hepatitis B vaccination program by active immunisation for infants.[11] This program for infants was introduced in 1989, even before the introduction of GHSSVH. The three doses of vaccination are given within 24 hours of birth, 1month and 6months of age. Although a seroprevalence study showed that the prevalence of hepatitis B surface antigen (HBsAg) in children born after the implementation of the program was lower than those born before (0.2% versus 1.08%),[12] there is still room for improvement as elimination of HBV infection as a public health threat requires a decrease in prevalence of HBsAg to below 0.1%.[3] This further reinforces the need for prophylactic AVT for HBsAg positive pregnant women with high viral load. Our study aims to compare the practice of prevention of MTCT of HBV in a tertiary referral liver centre before and after GHSSVH introduction.

MATERIALS AND METHODS

Study Design

This is a retrospective study performed in a tertiary referral liver centre in Malaysia. Total 1457 medical records of female with HBV infection from 1st January 2015 to 31st December 2019 were screened and patients fulfilling inclusion criteria were included. The inclusion criteria of the study were pregnant women with HBsAg positive or known to have HBV infection during the study period. We excluded patients with co-infections of other types of viral hepatitis or human immunodeficiency virus, concurrent liver diseases (e.g. autoimmune hepatitis, Wilson's disease), previous organ transplant and malignancy—except for hepatocellular carcinoma.

Data Collection

Electronic medical records were used to systematically identify patients using the diagnosis keyword "Hepatitis B" or "HBsAg positive" then filtered by gender and pregnancy status. Patients' demographics (age, ethnicity, parity and number of previous miscarriages) were recorded. Clinical features of patients during follow-up in outpatient clinic or inpatient reviews in ward were also recorded and divided into three parts: laboratory data, pregnancy-related comorbidities and HBV therapy. Laboratory data included platelet count, highest serum alanine aminotransferase (ALT) levels (normal value ≤33 U/L, abnormal value >33 U/L), highest serum aspartate aminotransferase (AST) levels (normal value ≤31 U/L, abnormal value >31 U/L), HBeAg status, HBeAb status and HBV DNA viral load. Prognostic scores of liver fibrosis via Fibrosis-4 (Fib-4) Score and AST to Platelet Ratio Index (APRI) Score were calculated.

Outcome Measurements and Endpoints

As GHSSVH was introduced in 2016, data collected were divided into two time epochs, 2015-2016 and 2017-2019. Primary outcomes were the percentage of pregnant mothers with HBV DNA > 200, 000 IU/ml on antiviral prophylaxis, with comparison being made between the two-time epochs. The secondary outcomes were to look at percentage of HBeAg-positive and HBeAg-negative patients with HBV DNA > 200, 000 IU/ml in this study population. This is to explore the possibility of initiation of antiviral prophylaxis based on HBeAg positive status as HBV DNA is a more cumbersome investigation.

Data Analysis

Statistical analyses were performed using IBM® Statistical Package for Social Sciences version 23.0 (SPSS, Chicago, IL). Numerical variables were presented using mean and standard deviation (SD) for normally distributed data while median and interquartile ranges (IQR) were additionally presented for non-normally distributed data. Comparison of data between 2015-2016 and 2017–2019 was determined using Pearson's chi-square test or Fischer's exact test for categorical data and Mann Whitney test for continuous data. The odds ratio (OR) and 95% confidence interval (CI) of pregnant women being on AVT when HBV DNA > 200, 000 IU/ml is derived using logistic regression analyses. All tests were two-sided and a $p<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of HBsAg positive Pregnant Women

This study included 117 HBsAg positive pregnancies (Table I). The median age was 32 years (interquartile range (IQR) 31 to 35). In the study population, 53.8% were Malay, 42.7% were Chinese while 3.4% were of other races including foreigners. Majority are Para 1 and primigravida.

During the follow-up, median highest ALT was 16 U/L (IQR 12–27) while median highest AST was 25 U/L (IQR 20 – 35). Among the pregnant women studied, 30.8% (n=36) were HBeAg positive while 23.1% (n=27) had HBV DNA > 200, 000 IU/ml. The median Fibrosis-4 (Fib-4) Score was 0.76 (IQR 0.59 to 1.15) while the median AST to Platelet Ratio Index (APRI) Score was 0.32 (IQR 0.24 to 0.47). None of the patients had liver cirrhosis or varices. One patient had both hepatocellular carcinoma and ascites.

Pregnancy-Related Comorbidities and Outcomes

Among the patients studied, 14 (12%) had anaemia in pregnancy, 24 (20.5%) had gestational diabetes, 6 (5.1%) had pre-eclampsia and 1 (0.9%) had placenta previa. Regarding pregnancy outcomes, 35 (29.9%) had lower segment caesarean section, 13 (11.1%) had pre-term delivery, 10 (8.5%) had low birth weight and 1 (0.9%) had birth defect (Table II).

Table I : Baseline characteristics of the study population (n = 117), 2015–2019

Characteristics	Value
Age in years, median (IQR)	32 (31–35)
Ethnicity, n (%)	
Malay	63 (53.8)
Chinese	50 (42.7)
Indian	0
Others	4 (3.4)
Parity, n (%)	
Missing data	1 (0.9)
0	27 (23.1)
1	30 (25.6)
2	20 (17.1)
3	24 (20.5)
4	7 (6.0)
≥5	8 (6.9)
Highest ALT during pregnancy	
Median (IQR)	16 (12–27)
Highest AST during pregnancy	
Median (IQR)	25 (20–35)
HBeAg status, n (%)	
Missing data	10 (8.5)
Negative	71 (60.7)
Positive	36 (30.8)
HBeAb status, n (%)	
Missing data	13 (11.1)
Negative	44 (37.6)
Positive	60 (51.3)
HBV DNA in IU/ml	
Missing data, N (%)	31 (26.5)
≤200,000, N (%)	59 (50.4)
>200,000, N (%)	27 (23.1)
Median (IQR)	566 (53 to 1,085,437)
Fibrosis-4 (Fib-4) Score	
Missing data, N (%)	27 (23.1%)
Median (IQR)	0.76 (0.59–1.15)
AST to Platelet Ratio Index (APRI) Score	
Missing data, N (%)	27 (23.1%)
Median (IQR)	0.32 (0.24–0.47)
Cirrhosis, n (%)	
Missing data	1 (0.9)
Not present	116 (99.1)
Present	0
Hepatocellular carcinoma, n (%)	
Missing data	9 (7.7)
Not present	107 (91.5)
Presents	1 (0.9)
Varices, n (%)	
Missing data	10 (8.5)
Not present	107 (91.5)
Present	0
Ascites, n (%)	
Missing data	3 (2.6)
Not present	113 (96.6)
Present	1 (0.9)

Table II: Pregnancy-related comorbidities and outcomes in study population (n = 117), 2015–2019

Comorbidities or Outcomes	Number (%)
Anaemia [a]	
Missing data	7 (6.0)
Not present	96 (82.1)
Present	14 (12.0)
Gestational diabetes	
Missing data	28 (23.9)
Not present	65 (55.6)
Present	24 (20.5)
Pre-eclampsia	
Missing data	27 (23.1)
Not present	84 (71.8)
Present	6 (5.1)
Placenta previa	
Missing data	26 (22.2)
Not present	90 (76.9)
Present	1 (0.9)
Lower segment C-section	
Missing data	33 (28.2)
No	49 (41.9)
Yes	35 (29.9)
Pre-term Delivery[b]	
Missing data	33 (28.2)
No	71 (60.7)
Yes	13 (11.1)
Low birth weight[c]	
Missing data	35 (29.9)
No	72 (61.5)
Yes	10 (8.5)
Birth defect	
Missing data	35 (29.9)
No	81 (69.2)
Yes	1 (0.9)

[a] Haemoglobin (Hb) <11 g/dl 1st trimester, Hb <10.5 g/dl 2nd trimester, Hb<10g/dL 3rd trimester [13]
[b] Delivery before 37weeks period of gestation[14]
[c] Birth weight < 2500g [15]

Table III: Cross-tabulation of HBV DNA level and HBeAg status versus AVT

	AVT during pregnancy	
	No	Yes
HBV DNA ≤200,000 IU/ml	56 (94.9%)	3 (5.1%)
HBV DNA >200,000 IU/ml	9 (33.3%)	18 (66.7%)
HBeAg Negative	66 (93.0%)	5 (7.0%)
HBeAg Positive	21 (58.3%)	15 (41.7%)

Table IV: Cross-tabulation of HBeAg status versus HBV DNA level ∧

HBeAg status:	HBV DNA level in IU/ml	
	≤200,000	>200,000
Negative	50 (92.6%)	4 (7.4%)
Positive	8 (27.6%)	21 (72.4%)

∧ Diagnostic accuracy values with HBV DNA level as the reference standard:
Sensitivity = 84.0% (63.1 to 94.7%)
Specificity = 86.2% (74.1% to 93.4%)
Positive predictive value = 72.4% (52.5 to 86.6%)
Negative predictive value = 92.6% (81.3 to 97.6%)
Positive likelihood ratio = 6.09 (3.12 to 11.85)
Negative likelihood ratio = 0.19 (0.08 to 0.46)

AVT for Hepatitis B

Majority, 95 (81.2%) had no AVT during pregnancy. One woman (0.9%) had AVT pre-pregnancy, but stopped during pregnancy while 3 (2.6%) had AVT before and during pregnancy. There were 18 (15.4%) patients who were newly started on AVT during pregnancy as prophylaxis.

About two-third, 18/27 (66.7%) of those with HBV DNA > 200, 000 IU/ml were on AVT during pregnancy. (Table III) The odds ratio of being on AVT for patients who had HBV DNA > 200, 000 IU/ml was 37.3 (95% CI 9.1 to 153.0). On the other hand, 3/59 (5.1%) of those whose HBV DNA ≤ 200, 000 IU/ml were on AVT. All of them were already on AVT prior to pregnancy, and the treatment was continued during pregnancy.

Table V: Comparison of 2015–2016 vs 2017–2019

Variables	2015–2016 (N = 39)	2017–2019 (N = 78)	*p* value
Age in years, median (IQR)	31 (29 to 33)	33 (31 to 36)	<0.001 [a]
Race, n (%)			1.000 b
Malay	21 (53.8)	42 (53.8)	
Chinese	17 (43.6)	33 (42.3)	
Indian	0	0	
Others	1 (2.6)	3 (3.8)	
Parity, n (%)			0.020 [b]
Missing data	1 (2.6)	0	
0	12 (30.8)	15 (19.2)	
1	4 (10.3)	26 (25.6)	
2	9 (23.1)	20 (17.2)	
3	10 (25.6)	24 (20.7)	
4	0	7 (9.0)	
≥5	3 (7.7)	5 (6.4)	
Number of miscarriages, n (%)			0.444 [b]
Missing data	1 (2.6)	0	
0	27 (69.2)	52 (66.7)	
1	8 (20.5)	17 (21.8)	
2	2 (5.1)	9 (11.5)	
5	1 (2.6)	0	
HBeAg status, n (%)			0.954 [b]
Missing data	3 (7.7)	7 (9.0)	
Negative	23 (59.0)	48 (61.5)	
Positive	13 (33.3)	23 (29.5)	
HBV DNA in IU/ml			0.801 [c]
Missing data, n (%)	13 (33.3)	18 (23.1)	
≤200,000, n (%)	17 (43.6)	42 (53.8)	
>200,000, n (%)	9 (23.1)	18 (23.1)	
Median (IQR)	1653 (115 to 12,434,917)	277 (22 to 461,895)	0.056 [a]
AVT during pregnancy, n (%)			0.799 [c]
No	33 (84.6)	63 (80.8)	
Yes	6 (15.4)	15 (19.2)	

p values are based on the following tests.
[a] Mann–Whitney test; [b] Fisher's exact test; [c] Chi-square test.

Among those with HBeAg positive status,15/36 (41.7%) were on AVT during pregnancy (Table III). On the other hand, 5/71 (7.0%) of those whose HBeAg-negative were on AVT. The odds ratio of being on AVT for patients who were HBeAg positive was 9.4 (95% CI 3.1 to 29.0).

Relationship of HBeAg Status to Hepatitis B Viral Load

Positive HBeAg predicted HBV DNA > 200, 000 IU/ml with a sensitivity of 84.0%, specificity of 86.2%, positive predictive value (PPV) of 72.4%, negative predictive value (NPV) of 92.6%, positive likelihood ratio of 6.09 and negative likelihood ratio of 0.19 (Table IV).

Comparison Between 2015–2016 and 2017–2019

There were 39 HBsAg positive pregnancies between 2015 and 2016 and 78 between 2017 and 2019 (Table V). The median age was 31 in the former group and 33 in the latter group. Thirteen (33.3%) in 2015–2016 group and 23 (29.5%) in 2017–2019 had HBeAg positive while 9 (23.1%) in 2015–2016 group and 18 (23.1%) in 2017–2019 had HBV DNA > 200,000 IU/ml. In 2015–2016, 5/9 (55.6%) of those with HBV DNA >200,000 IU/ml were on AVT during pregnancy, compared to 13/18 (72.2%) for 2017–2019, indicating that a patient has 58% higher odds (95% CI –63% to 568%) of being on AVT in 2017–2019 compared to 2015-2016 after accounting for HBV DNA level.

DISCUSSION

Our study found that HBsAg positive pregnant women with HBV DNA > 200,000 IU/ml have 58% higher odds of being on AVT in 2017–2019 compared to 2015–2016, although it is not statistically significant. This likely reflects changes in practice as increasing evidence is available regarding benefits and safety of short-term antiviral treatment to pregnant women with high viral load, in order to bring down the HBV DNA level for active and passive immunisation to be effective.

In parallel with this, many international guidelines are advocating perinatal antiviral prophylaxis as an additional measure to prevent MTCT of HBV. However, there are some variations in their recommendations. European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guideline recommends that all HBsAg positive pregnant women with HBV DNA > 200, 000 IU/ml or HBsAg > 4 $\log_{10}$ IU/ml should receive antiviral prophylaxis starting at 24–28 weeks of gestation.[16] The American Association for the Study of Liver Diseases (AASLD) 2018 and WHO (2020) recommend antiviral prophylaxis at a similar HBV DNA level, starting at 28 weeks of gestation.[3,17] On the other hand, the Asian Pacific Association for the Study of the Liver (APASL) 2016 recommends short term antiviral treatment to pregnant women at higher HBV DNA level threshold, at above above 6–7 $\log_{10}$ IU/ml from 28 to 32 weeks of gestation although it acknowledges that HBV infection can be transmitted even at

a lower HBV DNA level and that antiviral prophylaxis can be given after discussion with the patient.[18]

GHSSVH also provides doctors with an initial framework and goals to work on in order to attain WHO aim of achieving viral hepatitis elimination by 2030. It sets targets such as to achieve 50% coverage of prevention of MTCT of HBV by 2020 and 90% by 2030 as well as <1% prevalence of HBsAg positive among children by 2020 and <0.1% by 2030.[8] The availability of multiple guidelines which advocate antiviral prophylaxis in high viral load pregnant women likely increases the awareness of treating doctors to convince this group of patients for treatment and at the same time, pregnant women are more confident to accept antiviral prophylaxis.

However, it is worth pointing out that HBV DNA had 26.5% missing data while HBeAg status had 8.5% missing data in this study population. A possible explanation for this is HBeAg has shorter turn-around time and will be available earlier. Apart from that, HBV DNA is a more cumbersome test compared to HBeAg because HBV DNA is a quantitative virologic marker. Quantitative assaying of HBV requires expensive equipment and a contamination-free facility, and it cannot be routinely done in smaller hospitals serving rural communities.[19] Patients were referred to the tertiary referral liver centre from all over the country, which have different laboratory investigation capacity, and some may not have the availability of HBV DNA testing.

As such, this study also looks at the feasibility of using HBeAg positivity status for antiviral prophylaxis rather than high HBV DNA viral load. It was known that HBeAg positivity is a marker of high viral replication and may have a role in predicting risk of MTCT and the need for antenatal AVT.[20] In a retrospective study looking at predictive factors of high HBV DNA levels among women of reproductive-age group with Chronic Hepatitis B infection done by Khoo et al., it was found that HBeAg positive women had a 9.99-fold higher risk of showing HBV DNA > 200, 000 IU/ml compared to those who were HBeAg negative (AOR=9.99; 95% CI=5.50 to 18.13; p<0.001).[21] WHO also recommends that in low-income settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for antiviral prophylaxis in order to reduce MTCT of HBV.[3]

In this cohort of patients studied, a positive HBeAg predicted HBV DNA > 200,000 IU/ml with a sensitivity of 84.0%, specificity of 86.2%, positive predictive value (PPV) of 72.4%, negative predictive value (NPV) of 92.6%, positive likelihood ratio of 6.09 and negative likelihood ratio of 0.19. In a resource-limited setting, these values are acceptable, considering only 7.4% of those with negative HBeAg status have HBV DNA > 200,000 IU/ml. Similar results were obtained in a study by Thilakanathan et al., whereby a positive HBeAg provided sensitivity at 93.4% specificity at 92.3%, PPV at 78.6% and NPV at 97.9% for detection of HBV DNA ≥6 $\log_{10}$IU/mL.[22]

Alternatively, HBV DNA can be sent only for pregnant women who have positive HBeAg, which is estimated to account for about 20–55% of all HBsAg-positive women at child-bearing age. Such a testing protocol needs to be done earlier in pregnancy to ensure adequate time for subsequent HBV DNA level testing and initiation of AVT to achieve significant viral suppression before delivery.[5]

Based on our study, we recommend clear guidance and policy-driven care pathway for hepatitis B in pregnant women, starting with antenatal HBsAg screening, then further evaluation of HBsAg positive pregnant women for appropriate prophylaxis with antiviral and addition of passive hepatitis B immunisation to the babies born, in order to optimise prevention of MTCT of HBV. Detection of HBsAg positive pregnant woman is also an opportunity for contact tracing and bring to care other infected family or household members. Apart from that, our study found HBeAg positivity has high sensitivity, specificity and negative predictive value for HBV DNA > 200,000 IU/ml, making it possible to use HBeAg positivity status as guidance for antiviral prophylaxis to prevent MTCT of HBV, especially in healthcare set-up which has poor accessibilities for molecular testing laboratory.

Limitations of our study include the proportion of missing data in the study population, especially HBV DNA level, possibly due to late referral and this can be a potential bias. Although there is an increase in the percentage of pregnant women with HBV DNA > 200,000 IU/ml on prophylactic AVT after the introduction of GHSSVH, this study did not have adequate statistical power to show that it is statistically significant due to the small sample size. As this is a retrospective study, such limitations could not be avoided. Therefore, the generalisation of the study should be done with caution. However, these findings are useful preliminary data to show that as a tertiary referral liver centre, we have achieved WHO target of 50% coverage of prevention of MTCT by 2020. The information gathered may also guide future research on larger sample sizes and better study designs.

CONCLUSION

In conclusion, the introduction of GHSSVH and availability of vast evidence and guidelines advocating use of prophylactic AVT for HBsAg positive pregnant women with high viral load had positively affected the practice. HBeAg status can also serve as a potential alternative test in guiding antiviral prophylaxis for MTCT prevention. Nevertheless, a protocol on HBV management in pregnant women and education may enhance care in order to achieve WHO target of 90% coverage of prevention of MTCT of HBV and 0.1% prevalence on HBsAg among children by 2030.

ETHICAL APPROVAL

Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR ID-22-00620-51E). An informed consent waiver was approved in view of a non-intervention, retrospective study.

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Factors related to prehospital delay and decision delay among acute stroke patients in a district hospital, Malaysia

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ABSTRACT

Introduction: Time is the greatest challenge in stroke management. This study aimed to examine factors contributing to prehospital delay and decision delay among stroke patients.

Materials and Methods: A cross-sectional study involving acute stroke patients admitted to Seri Manjung Hospital was conducted between August 2019 and October 2020 via face-to-face interview. Prehospital delay was defined as more than 120 minutes taken from recognition of stroke symptoms till arrival in hospital, while decision delay was defined as more than 60 minutes taken from recognition of stroke symptoms till decision was made to seek treatment.

Results: The median prehospital delay of 102 enrolled patients was 364 minutes (IQR 151.5, 1134.3) while the median for decision delay was 120 minutes (IQR 30.0, 675.0). No history of stroke (adj. OR 4.15; 95% CI 1.21, 14.25; *p*=0.024) and unaware of thrombolysis service (adj. OR 17.12; 95% CI 1.28, 229.17; *p*=0.032) were associated with higher odds of prehospital delay, while Indian ethnicity (adj. OR 0.09; 95% CI 0.02, 0.52; *p*=0.007) was associated with lower odds of prehospital delay as compared to Malay ethnicity. On the other hand, higher National Institutes of Health Stroke Scale (NIHSS) score (adj. OR 0.86; 95% CI 0.78, 0.95; *p*=0.002) was associated with lower odds of decision delay.

Conclusion: Public awareness is crucial to shorten prehosital delay and decision delay for better patients' outcomes in stroke. Various public health campaigns are needed to improve the awareness for stroke.

KEYWORDS:
prehospital delay, decision delay, stroke, district hospital

INTRODUCTION

Stroke is a common neurological emergency that carries significant morbidity and mortality, and it is increasing over the years.[1] In Malaysia, stroke is the third leading cause of mortality from the year 2009 to 2020, with a staggering rate of 8.0% of mortality, compared to 15.0% for ischaemic heart disease.[2] Early presentation to hospitals has been shown to predict better functional outcomes in stroke patients. Intravenous thrombolysis within a time window of 3 to 4.5 hours of presentation of stroke have shown to improve the morbidity and mortality of stroke patients (number needed to treat, NNT = 10 – 21)[3] compared to antiplatelet therapy only. Mechanical thrombectomy has produced a better patient outcome with NNT of 3.[4] Better patient outcome was also observed even in those patients who came to hospital earlier but did not undergo thrombolysis or interventions.[5] These studies have clearly proven the adage saying "time is brain", emphasising time is of the essence in managing stroke patients to ensure the best outcomes.

Many efforts have been rolled out globally in order to minimise the delay of stroke patients in seeking medical treatment, but the results were often disappointing. This is owing to the fact that myriad factors are affecting prehospital delay in the presentation of patients to the hospital-like patients' help-seeking behaviour, stroke knowledge and socio-cultural background.[6] Lack of these local data poses great challenge in the mission of establishing more acute stroke-ready hospitals in district populations. To our knowledge, we have limited published data exploring the factors associated with prehospital delay in South-East Asian population, especially in Malaysia. Thus, this study aimed to examine how stroke patients in district setting in Malaysia react to stroke symptoms and factors that contributed to their prehospital delay and decision delay.

MATERIALS AND METHODS

This cross-sectional study was conducted from 1st August 2019 till 30th October 2020, involving 102 patients who were admitted to medical wards in Seri Manjung Hospital with diagnosis of acute stroke within 7 days of symptoms presentation. Seri Manjung Hospital is a non-neurologist acute stroke-ready hospital with Computed Tomography (CT) scan machine and thrombolysis service. It is located in Manjung province, Perak state, Malaysia with 258 000 semi-urban populations.

Patients were selected using non-probability convenience sampling method and approached by the investigators. Patients who met the inclusion criteria without violating the exclusion criteria were recruited in this study. The inclusion

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criteria were: (1) aged 18 and above; (2) presented with clinical features of stroke (ischaemic or haemorrhagic) confirmed by brain imaging. The exclusion criteria were: (1) Patients with stroke mimics and subarachnoid haemorrhage; (2) Patients who present to hospital more than 7 days after the onset of symptoms; (3) Patients who were unable to answer questions throughout hospital admission attributable to either impaired consciousness or neurological deficit; (4) Patients with cognitive impairment or psychiatric illness; (5) Patients who refuse consent for this study. Those who were eligible were interviewed face-to-face using a standardised questionnaire after written consent was obtained. The information comprised of patients' demographic profiles, comorbidities, prehospital details, stroke manifestations and patients' perceptions for stroke. Patients were asked to grade the severity of their symptoms as "mild" or "severe" based on how much the symptoms were affecting their function. In addition, the data on National Institutes of Health Stroke Scale (NIHSS) score and premorbid Modified Rankin Scale (mRS) score was collected by investigators using a standardised data collection form.

This study was approved by Medical Research Ethical Committee (KKM/NIHSEC/P19-1753(6)).

Stroke was diagnosed based on rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin[7], which was further confirmed by brain CT imaging.

Stroke subtypes were classified according to Oxfordshire Community Stroke Project (OCSP) system that include partial anterior circulation infarct (PACI), total anterior circulation infarct (TACI), lacunar infarct (LACI) and posterior circulation infarct (POCI).[8] The severity of stroke was measured using NIHSS scoring system.[9] Stroke symptoms were categorised by FAST (Facial asymmetry, Arms or lower limb weakness, Speech difficulty Test).[10] Prehospital delay was defined as the time taken from onset of symptoms till arrival to the emergency department of study hospital. Decision delay time was the time of recognition of stroke symptoms till decision was made to seek treatment, either from medical or non-medical personnel. Transport delay time was calculated from time of decision-making till arrival to hospital. Transport delay was not analysed in this study as it depends on the local geographical data, patients' accessibility to transport, emergency medical response and interfacility transfer, which were not studied in this research. If it was a wake-up stroke, we considered the time when patients first recognised their symptoms as the onset. When the time of symptom onset was recorded as "morning," "afternoon," "evening" or "night," we assumed the time of onset to be 8 AM, 12 PM, 3 PM, 9 PM, respectively.

The data collected were analysed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data and clinical profiles of study subjects were presented descriptively. Mean and standard deviation was used for normally distributed continuous data while median and interquartile range was used for non-normally distributed continuous data. Categorical data were reported as numbers and percentages.

In the analysis of factors related to prehospital delay, patients were dichotomised into non-prehospital delay (<120 minutes) and prehospital delay groups (>120 minutes). In the further subset analysis of decision delay, the patients were dichotomised into non-decision delay (<60 minutes) and decision delay (>60 minutes). These cut-off points were in reference to previous studies[11,12] and the consideration of the recommended thrombolysis time window of 3 hours and door-to-needle time for thrombolytic therapy (in-hospital delay) of $\leq$60 minutes.[13]

Logistic regression was used to identify variables independently associated with prehospital delay and decision delay, respectively. All variables with p value <0.25 in univariate analysis were included at the model entry for multivariate analysis. A stepwise approach was used to identify independent predictors of both prehospital delay and decision delay separately. The results of multiple logistic regression were reported as adjusted odd ratios with 95% CIs. A p value <0.05 was deemed significant.

RESULTS

Patients' Characteristics

A total of 102 patients were recruited in this study. Table I shows the characteristics and demographic profiles of the studied patients. The mean age of the patients was 59$\pm$12.7 years, and they were predominantly male (63.7%) and Malay ethnic (65.7%). The commonest underlying comorbid were hypertension (71.6%), followed by diabetes mellitus (38.2%), dyslipidemia (28.4%) and history of previous stroke (17.6%). One-fifth of the patients studied had no previously diagnosed comorbidity (20.6%). Majority of the patients had premorbid mRS of 0 (89.2%). During the data collection period, there was no patient with haemorrhagic stroke who fulfils the inclusion and exclusion criteria. LACI was the most prevalent (80.4%), followed by PACI (10.8%), POCI (5.9%) and TACI (2.9%), with the median NIHSS on admission of 5 (IQR 2.0, 8.0). All the patients have ischaemic stroke. Of 92 patients who presented with limb weakness, 59 of them perceived it as severe (57.8%). The number of patients who presented with severe facial asymmetry or severe dysarthria were 11 (10.8%) and 25 patients (24.5%), respectively. Other symptoms reported by patients included severe giddiness, gait instability, and disinhibition.

The median prehospital delay time was 364 minutes (IQR 151.5, 1134.3). A total of 80 patients (78.4%) arrived at study hospital more than 2 hours after the onset of stroke symptoms (delayed). The median decision delay time was 120 minutes (IQR 30.0, 675.0), of which 47 of the patients (46.1%) achieved equal or less than 60 minutes (non-delayed). Transport delay time showed a median of 161 minutes (IQR 80.0, 272.5), but this was not analysed in this study.

Majority of 55 out of 80 (68.8%) patients with prehospital delay had decision delay. It is worthy to note that in this study, all the patients with decision delay ended up with prehospital delay.

Only 39 patients (38.2%) perceived the symptoms as stroke. That left 20.6% of patients who did not think of stroke, and

Table I: Socio-demographic and clinical characteristics of enrolled patients (n=102)

Characteristics	n (%)
Age in years, Mean (SD)	59 (12.7)
Gender	
Male	65 (63.7)
Female	37 (36.3)
Ethnicity	
Malay	67 (65.7)
Chinese	26 (25.5)
Indian	7 (6.9)
Others	2 (1.9)
Comorbidities	
Hypertension	73 (71.6)
Diabetes mellitus	39 (38.2)
Dyslipidemia	29 (28.4)
Ischemic heart disease	15 (14.7)
Atrial Fibrillation	2 (1.9)
Congestive cardiac failure	2 (1.9)
Chronic kidney disease/end stage renal disease	4 (3.9)
Previous stroke	18 (17.6)
None	21 (20.6)
Subtype of stroke	
LACI	82 (80.4)
PACI	11 (10.8)
POCI	6 (5.9)
TACI	3 (2.9)
NIHSS Score, median (IQR)	5 (2.0, 8.0)
Symptoms	
Limb weakness	92 (89.3)
Mild	32 (31.4)
Severe	59 (57.8)
None	11 (10.8)
Facial asymmetry	31 (30.1)
Mild	20 (19.6)
Severe	11(10.8)
None	71 (69.6)
Dysarthria	56 (54.4)
Mild	31 (30.4)
Severe	25 (24.5)
None	46 (45.1)
Others*	7 (6.8)
Mild	4 (3.9)
Severe	3 (3.0)
None	95 (93.1)
Premorbid mRS Score	
0	91 (89.2)
1-2	5 (4.9)
3-5	6 (5.9)
Decision delay time in minutes, median (IQR)	120 (30.0, 675.0)
Transport delay time in minutes, median (IQR)	161 (80.0, 272.5)
Prehospital delay time in minutes, median (IQR)	364 (151.5, 1134.3)
Decision delay	
Delayed	55 (53.9)
Non-delayed	47 (46.1)
Prehospital delay	
Delayed	80 (78.4)
Non-delayed	22 (21.6)
Types of first helper	
Family members and relatives	83 (81.4)
Friends	10 (9.8)
Emergency medical services	7 (6.9)
Self	2 (1.9)
Medical contact(s) before study hospital	
***may choose more than 1**	
None, straight to study hospital	48 (47.1)
Basic care hospital	9 (8.8)
Health clinic	23 (22.5)
General practitioner clinic	21 (20.6)
Traditional medicine	1 (1.0)
Haemodialysis centre	1 (1.0)
Pharmacy	1 (1.0)

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Table I: Socio-demographic and clinical characteristics of enrolled patients (n=102)

Characteristics	n (%)
Number of stops before study hospital	
0	48 (47.1)
1	52 (51.0)
2	2 (1.9)
Reason for decision delay	
Mild symptoms	23 (33.8)
Non-progressive symptoms	7 (10.3)
Not perceived as stroke	11 (16.2)
Unable to get help	13 (19.1)
Unconscious	2 (2.9)
Others**	27 (39.7)
Perception of Stroke	
Yes	39 (38.2)
No***	21 (20.6)
Not sure***	42 (41.2)
Awareness of thrombolysis service	
Yes	4 (3.9)
No	98 (96.1)

SD, Standard deviation; IQR, Interquartile range; LACI, Lacunar infarct; PACI, Partial anterior circulation infarct; POCI, Posterior circulation infarct; TACI, Total anterior circulation infarct; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale
*Other symptoms include: Giddiness, disinhibition, unsteady gait.
**Other reasons for decision delay include: Symptoms perceived as self-limiting, fear of hospital treatment, not knowing what to do.
***Other perceptions towards the presenting symptoms include: non-medical causes (e.g. being exhausted, weather or dietary causes), musculoskeletal injury, psychological effect and other non-scientific causes.

41.2% was unsure of reason. Only 4 patients (3.9%) were aware of thrombolysis treatment in stroke. There were 81.4% of patients who first sought help from family members or relatives, followed by friends (9.8%). Merely 6.9% of the patients actually called for EMS. Slightly less than half of these patients (47.1%) went straight to the study hospital; there were 43.1% went to health clinics or general practitioner clinics, and 8.8% went to a basic care hospital (without CT facility). The reasons for their decision delay included symptoms being mild, unable to get help, symptoms being perceived as self-limiting and not knowing how to react.

Factors Associated with Prehospital Delay

Table II shows the univariate and multivariate logistic regression analyses of factors predicting prehospital delay. In the univariate analyses, Indians had lower odds of prehospital delay as compared to Malays (OR=0.12, 95% CI 0.02, 0.61; *p*=0.011). Patients with no history of stroke were more likely to have prehospital delay as compared to those with previous stroke (OR=4.00, 95% CI 1.34, 11.93; *p*=0.013). Prehospital delay was higher among patients who were unsure of having stroke attack as compared to those who were certain of having a stroke episode (OR=3.00, 95% CI 1.01, 8.93; *p*=0.048) and patients who were not aware of thrombolysis service as compared to those who were aware (OR=12.47, 95% CI 1.23, 126.66; *p*=0.033). Patients who had a detour before presenting to study hospital also had higher odds of prehospital delay as compared to those who went directly to stroke ready hospital (OR=2.92, 95% CI 1.07, 7.97; *p*=0.036). The multivariate analyses for prehospital delay retained two positive predictors: no previous stroke (adj. OR=4.15, 95% CI 1.21, 14.25; *p*=0.024) and not being aware of thrombolysis service (adj. OR=17.12, 95% CI 1.28, 229.17; p=0.032), and one negative predictor: Indian ethnicity (adj. OR=0.09, 95% CI 0.02, 0.52; *p*=0.007).

Factors Associated with Decision Delay

Table III shows the univariate and multivariate logistic regression analyses of factors predicting decision delay. Only NIHSS score was significantly associated with decision delay in which higher NIHSS score (adj. OR=0.86, 95% CI 0.78, 0.95; *p*=0.002) was associated with lower odds of decision delay.

DISCUSSION

Definition of prehospital delay in our study was relatively consistent with previous studies, but decision delay was defined differently. Decision delay cut-off was taken as 60 minutes in most studies, but some definitions were inclusive of the time till help arrived.[12,15-16] The definitions of decision time delay in wake-up strokes were also different as the onset of stroke symptoms was defined as the time at which the patients last known to be well before sleep.[12,15] We considered the time of awareness of symptoms as the earliest time to seek help, which is a more sensible starting point to examine the patients' responsiveness.[16]

The median decision delay time we reported in study (120 minutes) is similar in other developed countries.[17] In a study by Carroll et al, the median time for patients to decide to call for help after experiencing symptoms was 30 minutes. Majority of the studies showed less than half of the stroke patients actually arrived at hospital within 3 hours.[17] Previous studies have shown that decision delay has been a significant factor to be considered in prehospital delay in the presentation of stroke patients to hospital for treatment.[15] This is similar to the finding in our study.

Prior stroke experience may have taught patients to take a more direct path to the hospital, resulting in less prehospital delay among those who had a history of stroke, but there is

Table II: Univariate and multivariate analysis of factors related to prehospital delay

Variable	Prehospital delay, n (%)		Univariate analysis			Multivariate analysis		
	No	Yes	Crude OR	95% CI	*p* value[a]	Adj. OR	95% CI	*p* value[b]
Age in years, mean (SD)	60 (8.9)	59 (13.6)	1.00	(0.96, 1.03)	0.787			
Gender								
Male	14 (63.6)	51 (63.8)	1.00	(0.38, 2.68)	0.992			
Female	8 (36.4)	29 (36.2)	1.00					
Ethnicity					0.032			0.019[†]
Malay	9 (40.9)	58 (72.5)	1.00			1.00		
Chinese	8 (36.4)	18 (22.5)	0.35	(0.12, 1.04)	0.058	0.36	(0.11, 1.24)	0.105
Indian	4 (18.2)	3 (3.8)	0.12	(0.02, 0.61)	0.011	0.09	(0.02, 0.52)	0.007[†]
Others	1 (4.5)	1 (1.2)	0.16	(0.01, 2.71)	0.202	0.05	(0.00, 1.05)	0.054
Comorbidity								
Hypertension								
No	6 (27.3)	23 (28.8)	1.08	(0.37, 3.09)	0.892			
Yes	16 (72.7)	57 (71.2)	1.00					
Diabetes Mellitus								
No	12 (54.6)	51 (63.8)	1.47	(0.56, 3.81)	0.433			
Yes	10 (45.4)	29 (36.2)	1.00					
Dyslipidaemia								
No	13 (59.1)	60 (75.0)	2.08	(0.77, 5.59)	0.148			
Yes	9 (40.9)	20 (25.0)	1.00					
Ischemic heart disease								
No	19 (86.4)	68 (85.0)	0.90	(0.23, 3.50)	0.873			
Yes	3 (13.6)	12 (15.0)	1.00					
Atrial fibrillation								
No	21 (95.5)	79 (98.8)	3.76	(0.23, 62.69)	0.356			
Yes	1 (4.5)	1 (1.2)	1.00					
Congestive cardiac failure								
No	22 (100.0)	78 (97.5)	0.00	(0.00, -)	0.999			
Yes	0 (0.0)	2 (2.5)	1.00					
Chronic kidney disease/end stage renal failure								
No	22 (100.0)	76 (95.0)	0.00	(0.00, -)	0.999			
Yes	0 (0.0)	4 (5.0)	1.00					
Previous stroke								
No	14 (63.6)	70 (87.5)	4.00	(1.34, 11.93)	0.013	4.15	(1.21, 14.25)	0.024[†]
Yes	8 (36.4)	10 (12.5)	1.00			1.00		
No comorbid								
No	19 (86.4)	62 (77.5)	1.00	(0.49, 6.92)	0.368			
Yes	3 (13.6)	18 (22.5)	1.84		0.205			
Diagnosis								
LACI	15 (68.2)	67 (83.8)	1.00					
PACI	4 (18.2)	7 (8.8)	0.40	(0.10,1.51)	0.174			
POCI	1 (4.5)	5 (6.2)	1.12	(0.12, 10.30)	0.921			
TACI	2 (9.1)	1 (1.2)	0.11	(0.01, 1.32)	0.082			
NIHSS Score, median (IQR)	5.5 (2.0, 11.3)	5 (2.0, 7.0)	0.91	(0.84, 1.00)	0.050	0.90	(0.80, 1.00)	0.057
Premorbid MRS Score					0.592			
0	19 (86.4)	72 (90.0)	1.00					
1-2	2 (9.1)	3 (3.8)	0.40	(0.06, 2.54)	0.329			
3-5	1 (4.5)	5 (6.2)	1.32	(0.15, 11.98)	0.805			
Types of helper					0.884			
Family members and relatives	17 (77.3)	66 (82.5)	1.66	(0.39, 7.12)	0.492			
Friends	3 (13.6)	7 (8.8)	1.00					
Emergency medical services	2 (9.1)	5 (6.2)	1.07	(0.13, 8.98)	0.949			
Self (No helper)	0 (0.0)	2 (2.5)	$6x10^8$	(0.00, -)	0.999			

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Table II: Univariate and multivariate analysis of factors related to prehospital delay

Variable	Prehospital delay, n (%)		Univariate analysis			Multivariate analysis		
	No	Yes	Crude OR	95% CI	*p* value[a]	Adj. OR	95% CI	*p* value[b]
Symptoms								
Limb weakness					0.876			
Mild	7 (31.8)	25 (31.2)	1.34	(0.28, 6.43)	0.715			
Severe	12 (54.6)	47 (58.8)	1.47	(0.34, 6.39)	0.608			
None	3 (13.6)	8 (10.0)	1.00					
Facial asymmetry					0.369			
Mild	3 (13.6)	17 (21.2)	1.93	(0.51, 7.34)	0.338			
Severe	1 (4.6)	10 (12.5)	3.40	(0.41, 28.41)	0.259			
None	18 (81.8)	53 (66.3)	1.00					
Dysarthria								
Mild	8 (36.4)	23 (28.8)	0.70	(0.24, 2.07)	0.790			
Severe	5 (22.7)	20 (25.0)	0.97	(0.29, 3.30)	0.518			
None	9 (40.9)	37 (46.2)	1.00		0.965			
Other symptoms								
Mild	0 (0.0)	4 (5.0)	$4x10^8$	(0.00, -)	0.273			
Severe	2 (9.1)	1 (1.2)	0.13	(0.01, 1.55)	0.999			
None	20 (90.9)	75 (93.8)	1.00		0.107			
Perception of Stroke					0.085			
Yes	13 (59.1)	26 (32.5)	1.00					
No	3 (13.6)	18 (22.5)	3.00	(0.75, 12.07)	0.122			
Unsure	6 (27.3)	36 (45.0)	3.00	(1.01, 8.93)	0.048			
Awareness of thrombolysis service								
Yes	3 (13.6)	1 (1.2)	1.00			1.00		
No	19 (86.4)	79 (98.8)	12.47	(1.23,126.66)	0.033	17.12	(1.28, 229.17)	0.032†
Medical contact(s) before study hospital								
Health Clinic								
Yes	5 (22.7)	18 (22.5)	1.00					
No	17 (77.3)	62 (77.5)	1.01	(0.33, 3.13)	0.982			
GP Clinic								
Yes	0 (0.0)	21 (26.2)	1.00					
No	22(100.0)	59 (73.8)	0.00	(0.00, -)	0.998			
Basic care hospital								
Yes	2 (9.1)	7 (8.8)	1.00					
No	20 (90.9)	73 (91.2)	1.04	(0.20, 5.42)	0.960			
Traditional Medicine								
Yes	0 (0.0)	1 (1.2)	1.00					
No	22 (100.0)	79 (98.8)	0.00	(0.00, -)	1.000			
Other Stops*								
Yes	0 (0.0)	2 (2.5)	1.00					
No	22 (100.0)	78 (97.5)	$1x10^9$	(0.00, -)	0.999			
Number of stops before study hospital					0.111			
0	15 (68.2)	33 (41.2)	1.00					
1	7 (31.8)	45 (56.3)	2.92	(1.07, 7.97)	0.036			
2	0 (0.0)	2 (2.5)	$7x10^8$	(0.00, -)	0.999			

OR, Odd ratio; Adj. OR, Adjusted odd ratio; CI, Confidence interval; SD, Standard deviation; IQR, Interquartile range; LACI, Lacunar infarct; PACI, Partial anterior circulation infarct; POCI, Posterior circulation infarct; TACI, Total anterior circulation infarct; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale

[a] Wald test

[b] Wald test; stepwise method for multivariable analysis was employed. The *p* value of only significant variables of the multivariable analysis were presented in the table

*Other stops prior to study hospital includes HD centre and pharmacy

† denotes significant *p* value of <0.05

no significantly less decision delay. The plausible explanation to this phenomenon is the failure to apply knowledge into action even though an individual might have been exposed to stroke education previously, leading to the psychology of believing in "lightning does not strike twice". It was also worrisome to see there was no difference in the decision time in those who already had at least one cardiovascular risk factor. This finding is similar to Ashraf et al[18] and Faiz et al[15], suggesting the lack of knowledge of primary stroke prevention for patients who are at risk of stroke.

Although our study showed that the severity of stroke by NIHSS (clinicians' judgement) was associated with less decision delay, no association was found with the severity of patient-reported FAST symptoms (patients' judgement) and

Table III: Univariate and multivariate analysis of factors related to decision delay

Variable	Decision delay, n (%)		Univariate analysis			Multivariate analysis		
	No	Yes	Crude OR	95% CI	*p* value[a]	Adj. OR	95% CI	*p* value[b]
Age in years, mean (SD)	61 (12.8)	58 (12.6)	0.98	(0.95, 1.01)	0.163			
Gender								
Male	27 (57.4)	38 (69.1)	1.66	(0.73, 3.73)	0.224			
Female	20 (42.6)	17 (30.9)	1.00					
Ethnicity					0.600			
Malay	29 (61.7)	38 (69.1)	1.00					
Chinese	12 (25.5)	14 (25.5)	0.89	(0.36, 2.21)	0.802			
Indian	5 (10.7)	2 (3.6)	0.31	(0.06, 1.69)	0.174			
Others	1 (2.1)	1 (1.8)	0.76	(0.05, 12.72)	0.851			
Comorbidity								
Hypertension								
No	12 (25.5)	17 (30.9)	1.31	(0.55, 3.12)	0.549			
Yes	35 (74.5)	38 (69.1)	1.00					
Diabetes mellitus								
No	29 (61.7)	34 (61.8)	1.01	(0.45, 2.24)	0.990			
Yes	18 (38.3)	21 (38.2)	1.00					
Dyslipidaemia								
No	32 (68.1)	41 (74.5)	1.37	(0.58, 3.25)	0.472			
Yes	15 (31.9)	14 (25.5)	1.00					
Ischaemic heart disease								
No	38 (80.9)	49 (89.1)	1.93	(0.63, 5.91)	0.247			
Yes	9 (19.1)	6 (10.9)	1.00					
Atrial fibrillation								
No	45 (95.7)	55 (100.0)	$2x10^9$	(0.00, -)	0.999			
Yes	2 (4.3)	0 (0.0)	1.00					
Congestive cardiac failure								
No	46 (97.9)	54 (98.2)	1.17	(0.07, 19.30)	0.911			
Yes	1 (2.1)	1 (1.8)	1.00					
Chronic kidney disease/end stage renal failure								
No	45 (95.7)	53 (96.4)	1.18	(0.16, 8.70)	0.873			
Yes	2 (4.3)	2 (3.6)	1.00					
Previous stroke								
No	36 (76.6)	48 (87.3)	2.10	(0.74, 5.94)	0.164			
Yes	11 (23.4)	7 (12.7)	1.00					
No comorbid								
No	32 (83.0)	42 (76.4)	1.00					
Yes	8 (17.0)	13 (23.6)	1.51	(0.57, 4.03)	0.412			
Subtypes of stroke					0.587			
LACI	34 (72.3)	48 (87.3)	1.00					
PACI	7 (14.9)	4 (7.3)	0.41	(0.11, 1.49)	0.174			
POCI	3 (6.4)	3 (5.4)	0.71	(0.14, 3.72)	0.684			
TACI	3 (6.4)	0 (0.0)	0.00	(0.00, -)	0.999			
NIHSS Score, median (IQR)	6 (3.0, 10.0)	4 (2.0, 6.0)	0.86	(0.78, 0.95)	0.002	0.86	(0.78, 0.95)	0.002†
Premorbid mRS Score					0.796			
0	41 (87.2)	50 (90.9)	1.00					
1-2	3 (6.4)	2 (3.6)	0.55	(0.09, 3.43)	0.519			
3-5	3 (6.4)	3 (5.5)	0.82	(0.16, 4.28)	0.814			
Symptoms								
Limb weakness					0.703			
Mild	14 (29.8)	18 (32.7)	0.74	(0.18, 3.02)	0.669			
Severe	29 (61.7)	30 (54.6)	0.59	(0.16, 2.24)	0.439			
None	4 (8.5)	7 (12.7)	1.00					
Facial asymmetry								
Mild	10 (21.3)	10 (18.2)	0.87	(0.32, 2.34)	0.763			
Severe	4 (8.5)	7 (12.7)	1.52	(0.41, 5.66)	0.781			
None	33 (70.2)	38 (69.1)	1.00		0.532			
Dysarthria					0.892			
Mild	15 (31.9)	16 (29.1)	0.82	(0.33, 2.05)	0.672			
Severe	12 (25.5)	13 (23.6)	0.83	(0.31, 2.22)	0.715			
None	20 (42.6)	26 (47.3)	1.00					
Other symptoms					1.000			
Mild	0 (0.0)	4 (7.3)	$1x10^9$	(0.00, -)	0.999			
Severe	3 (6.4)	0 (0.0)	0.00	(0.00, -)	0.999			
None	44 (93.6)	51 (92.7)	1.00					
Perception of Stroke					0.710			
Yes	20 (42.6)	19 (34.6)	1.00					
No	18 (38.3)	24 (43.6)	1.40	(0.48, 4.09)	0.534			
Unsure	9 (19.1)	12 (21.8)	1.40	(0.59, 3.37)	0.448			
Awareness of thrombolysis service								
No	44 (93.6)	54 (98.2)	3.68	(0.37, 36.65)	0.266			
Yes	3 (6.4)	1 (1.8)	1.00					

OR, Odd Ratio; Adj. OR, Adjusted Odd Ratio; CI, Confidence Interval; SD, Standard Deviation; IQR, Interquartile Range; LACI, Lacunar infarct; PACI, partial anterior circulation infarct; POCI, Posterior circulation infarct; TACI, Total anterior circulation infarct; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.

[a] Wald test

[b] Wald test; Stepwise method for multivariable analysis was employed. The *p* value of only significant variables of the multivariable analysis were presented in the table

† denotes significant *p* value of <0.05

less decision delay. This reflects the poor level of awareness and knowledge for stroke among our study population, and this does not differ among different age groups, genders or ethnicity. In this report, the level of stroke awareness among our patients concurred with earlier findings by Carroll et al, who reported only 40% of stroke patients were able to identify their diagnosis.[14] Moreover, these stroke symptoms were attributed by patients to other non-stroke causes, over which patients perceive control, causing a significant decision delay.[18] With the advent of intravenous thrombolysis and mechanical thrombectomy in acute stroke, it is crucial that patients should take the shortest time straight to an acute stroke-ready hospital. Another novel finding in our study indicated only a small number of patients came to hospital using EMS. Majority of patients sought help from the nearest family members, friends or relatives. The impact of EMS in reducing prehospital delay is inconsistent across different studies[12,19], partly because it depends on the local geographical factor and medical infrastructures.

Patients' awareness and knowledge for stroke is one of the biggest obstacles to shorten prehospital delay, but it is believed there is more to it. Previous studies have shown even good knowledge of stroke symptoms is insufficient as there was a significant discrepancy between awareness and action taken following stroke.[12,14,20] In our study, less than half of the patients were unable to recognise FAST as stroke. However, patients who have correctly identified stroke do not have significant shorter prehospital or decision delay. The mnemonic FAST has been a sensitive tool for detecting stroke in prehospital setting.[21-22] Although over the years, public health campaigns have been held to publicise this knowledge, the impact on prehospital delay was minimal, most probably due to the limited behavioural impact of these health campaigns.[23-24] Therefore, future research is needed to formulate more sustainable, multi-levelled, practicable health education strategies, for example school education[25], mass media[26] and behavioural intervention programs.[27]

The limitation of our study is being single-centred cross-sectional study, which focused only in a suburban area. The study population did not reflect true incidence of stroke owing to the sampling method and exclusion of patients with severe stroke who were unable to accept the interviews. We focussed in evaluating stroke patients' first-person perception and experience, instead of third-person perspective i.e. bystanders or caregivers, hence we excluded patients who were not fit to be interviewed. The small sample size and non-probability sampling method in this study might introduce selection bias, particularly in the findings on ethnicity and awareness of thrombolysis therapy. Other biases that may occur include recall bias by study subjects in estimating response time and the perception bias in responding towards open-ended interview questions. A multi-centred analysis with a larger sample size using the probability sampling method is recommended in the future to overcome these limitations for a more generalisable and representative results.

CONCLUSION

Our research provides evidence that there was a substantial lack of knowledge and lacklustre response to stroke among our studied populations. Various strategies are required in the future not only to disseminate knowledge of stroke, but also to modulate the public behaviour and rectify the misperception for stroke as these represent the main obstacles towards early hospital presentation and stroke-directed treatment.

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DISCLOSURE

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

The impact of cleft lip and palate on the quality of life of young children: A scoping review

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ABSTRACT

Introduction: Cleft lip and palate (CL/P) are among the most common congenital abnormalities. The purpose of the present study was to review the literature relating to the quality of life (QoL) in young patients with cleft lip and/or palate (CL/P) and to identify the specific aspect of QoL in young patients with CL/P that is mostly affected. Other associated variables within studies that may have an impact on QoL were also identified.

Materials and Methods: Systematic searches of PubMed, Scopus and Web of Science databases were conducted. Independent reviewers screened the title, abstract and full texts according to predetermined inclusion and exclusion criteria. Articles published in English from January 2012 to March 2022 reporting the QoL of non-syndromic young patients aged 7–18 years with CL/P were included. Review articles and articles reporting the psychological adjustment of parents or other family members with CL/P were excluded.

Results: 975 publications were identified, of which 20 studies met our inclusion criteria. The majority of studies reported that the CL/P condition has a negative impact on the QoL. Psychological health, functional well-being, social-emotional well-being and school environment are domains that are affected. Compared with typically developing young patients, those with CL/P had lower QoL scores even though QoL was assessed using different instruments across studies. The impact of CL/P on overall QoL scores varied by age but not gender or cleft type.

Conclusion: Our reviews had shown the presence of CL/P negatively affects the QoL of young patients. Psychological health is the most affected QoL domain. Understanding the impacted domain will help in planning and delivering better health care for individuals with CL/P and reducing the stigma commonly associated with CL/P. Future studies should target intervention on psychological health and consider resilience factors towards positive adjustment.

KEYWORDS:
Quality of life, cleft lip, cleft palate, congenital, children, adolescents

INTRODUCTION

Cleft lip and palate (CL/P) are among the most common congenital abnormalities, with an overall worldwide prevalence of 1 per 1,000 births.[1] The management of CL/P is long-term, beginning from birth and continuing into early adulthood. While a child born with CL/P faces a visible facial disfigurement, they also encounter other issues related to the cleft such as feeding, hearing, speech and language difficulties that compromise their overall ability to communicate effectively. Young patients with CL/P are at greater risk of developing psychological problems due to the various issues associated with having cleft.[2,3] Some contributing factors include parental stress and worry,[4] difficulties coping with academic demands,[5] and being teased or bullied due to having visible differences and speech and hearing difficulties.[6]

The distress may manifest itself through various psychological and psychosocial problems such as anxiety and depression, emotional and behavioural issues, poor social skills, social withdrawal, poor self-concept and lower self-esteem. These problems become more apparent at schoolage as physical aesthetic and speech quality becomes the key factors to successful social interaction and acceptance among peers.[7] Young patients with CL/P, especially the ones with visible facial asymmetries and scarring, may face social rejection, experience more events of teasing and bullying at school, and have a lower quality of life (QoL) score when compared to those with less visible cleft features, as seen in cases of cleft palate only.[5,8] Unfortunately, being teased or bullied has been linked to poorer psychosocial adjustments; increasing the likelihood of developing psychiatric-related issues later in life.[9,10]

Previous studies have shown that young patients with CL/P have a poor health-related QoL compared to unaffected peers,[11-14] albeit not always consistently.[15,16] These inconsistent findings may be attributed to factors such as sample size, place of study and the involvement of multidisciplinary care and support from a psychological team or lack thereof.[17-20] For example, Tannure et al.[16] showed that delivering psychological and surgical intervention during early childhood improved the QoL of both patients and their caregivers.

In the past decade, two systematic reviews have been conducted by Klassen et al.[21] and Herkrath et al.[22] on the QoL of young patients with CL/P. Klassen et al.[21] identified health concepts and determinants of QoL in individuals with CL/P and outlined a conceptual framework of QoL that includes physical, psychological and social health. This review found that while several domains such as physical health, self-esteem, psychological distress and peer relation are well-researched among affected individuals, other areas such as

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family function, social function, social support and school function remained poorly studied.[21] Klassen et al.[21] also identified several instruments used to assess QoL in young patients with CL/P, such as the Youth Quality of Life Instrument-Craniofacial Surgery (YQoL-CS) and Child Oral Health Quality of Life Questionnaire (COHQoL). Importantly, they noted that these questionnaires focussed broadly on craniofacial conditions and did not include specific concerns of young patients with CL/P conditions.[21] On the other hand, Herkrath et al.[22] focussed on the QoL of young patients with nonsyndromic CL/P and reported that CL/P negatively affects the QoL in at least one domain with emotional and functional well-being as the most affected domains and social dimension as the least affected.

Identifying predictors of QoL and associated risks factor is essential in planning and delivering better health care for individuals with CL/P and reducing the stigma commonly associated with CL/P.[23,24] However, while the earlier reviews by Klassen et al.[21] and De Queiroz Herkrath et al.[25] made a significant contribution towards this goal, neither reported the impact of CL/P on QoL by age, gender or type of cleft. Therefore, the purpose of this review is to (1) systematically review the literature relating to the QoL in young patients with cleft lip and/or palate CL/P and (2) to identify the specific aspect of QoL in young patients with CL/P such as age, gender and cleft types that may have an impact on specific QoL domains (oral health, functional well-being and social-emotional) that is mostly affected.

MATERIALS AND METHODS

This scoping review was conducted based on the five-stage methodological framework proposed by Arksey and O'Malley.[26] The five stages include (1) identifying the research questions, (2) identifying relevant studies, (3) study selection, (4) charting the data and (5) collating, summarising and reporting the results.

Inclusion Criteria

Original articles reporting the QoL of patients aged 7–18 years with CL/P were included to assess the impact of CL/P conditions on school-aged patients specifically. Throughout the manuscript, the terms young patient with CL/P were used to avoid confusion with children and adolescent-specific definitions in the result later on. Convention on the Rights of the Child (CRC), defined a child as *"every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier"*.[27] However in this review paper, we are interested in children aged 7–18 years old. Relevant studies published in English from January 2012 to March 2022 utilising quantitative, qualitative or mixed-method modalities were considered. In addition, studies with any reporting modality, including self-reports, parent reports and third-party reports (such as those obtained via clinicians, laypersons and teachers), were included.

Exclusion Criteria

Literature reviews, systematic reviews, meta-analyses, summary articles, book chapters, case studies, letters, comments, editorials and unpublished dissertations published during the search period were excluded. Articles relating to other physical disfigurements of cleft lip and palate were excluded. Also, articles reporting the psychological adjustment of parents or other family members with CL/P were excluded as this study aimed to examine only the QoL of children with CL/P. Articles reporting 'late presentation' for cleft repair in children, adolescents, young adults or adults were excluded since the findings are not equivalent to routine treatment. Finally, articles that did not differentiate the results of nonsyndromic CL/P and syndromic children were excluded.

Search Strategy

Three online databases (PubMed, Scopus and Web of Sciences) were searched in March 2022 to identify potentially relevant articles. The search string used was ("cleft lip palate" OR "cleft lip" OR "cleft palate") AND ("quality of life") AND (children OR teenager OR youth OR adolescent). No articles were recovered from grey literature.

Study Selection Process

During the study selection process, inclusion and exclusion criteria were used to select the study in line with scoping review method. Abstracts were obtained for all the studies identified during electronic searches. Two reviewers (SY and HM) independently screened the title, abstracts and full-text copies to eliminate articles that failed to meet eligibility criteria.

Charting the Data

A data extraction form was created using commercial spreadsheet software (Microsoft Excel™365, Microsoft, Inc., Redmond, WA, USA) by SY to summarize the data. Only articles meeting the inclusion criteria were included in reviews. The reviewers discuss whether the data being extracted answered research questions. Following revisions, the final data charted were: author (s), age range, sample size, types of cleft, instruments used, informant type, consensus, determinant, reported negative influence in CL/P and associated factors.

RESULTS

The electronic search generates 975 results. After removing duplicates, 532 unique articles were identified. Title and abstract screening resulted in the exclusion of 455 articles. The full texts of 77 articles were retrieved and another 57 articles were excluded after full-text screening for not meeting the inclusion criteria. Finally, 20 articles were included in this scoping review (Table I). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[28] was adapted for use in this scoping review (Figure 1).

Due to different instruments being used to access QoL across studies, a narrative approach was used to report the findings of the included studies. The results and conclusion of this review are presented by highlighting any statistically significant findings reported from original articles.

Respondents

The study population in 11 out of the 20 studies (55%) included in this review comprised young patients with CL/P (mean age=12.8 years),[12,29-38] while nine studies (45%) involved child–parent dyad.[13,18-20,39-43] Seven studies reported similar findings or no statistically significant differences

Table I: Characteristics of the studies included in the review

No	Author	Cleft/ control (N)	Age range; types of cleft	QOL instruments, informant, correlation/consensus	Determinants	Impacted domain
1	Oka (29)[a]	69	11–18 ; CL, CP	YQOL-FD, children	Age; sex; cleft types	• Negative consequence and stigma • Age (significant)
2	Ali (39)[a]	70	8–16 ; CLP	COHIP, Children, and caregiver, significant differences	Children and parents	• Caregiver and children rating (overall score and oral symptoms)
3	Ali (30)[a]	75/150	8–16 ; CLP	COHIP, children	Age; gender; peers, cleft types	• Peers (overall score)
4	Fowler (40)[a]	174	8–13 CP, CLP	CPQ & Parent Version (P-CPQ); children and parents; good correlation (r= 0.97)	Sex, Ethnicity, cleft phenotype	• Not significance on total score • Cleft phenotype (not significance – CLP had a higher score compared to CP • Ethnicity (significance- the pacific island had a higher score)
5	Aleksieva (31)[a]	91/790	CLP: 12.74 ± 1.86 Control: 12.76 ±1.26; CL, CP, CLP	CPQ, children	Cleft and control, self-esteem	• Cleft phenotype • Self-esteem did not differ in significance for both groups except for behavioral conduct and scholastic competence • higher self-esteem in cleft groups
6	Lin (13)[a]	120	8–15; CL, CP, CLP	COHIP, children and parents, weak-moderate correlation	Age, gender; cleft types, parents	• Cleft types • Gender • Age
7	Crepaldi (32)	57	14–17; CL, CP,CLP	SF-36, children	CLP types, age, gender	• Not significantwhen compared between age and gender • Gender (female lower score in Bodily pain, vitality, and mental health) • Cleft type (CL and CP lower score of HRQOL than CLP in domain: limitation)
8	Nolte (41)	170	8–18; CL, CP, CLP	COHIP, children and parents, a significant difference in oral symptoms and functional well-being only	Gender, parents, cleft types	
9	Nagappan (33)[a]	80/80	8–16; CL, CP,	COHIP, children	Cleft and control	• Functional well-being • Social/ emotional well-being, • School environment
10	Abebe (19)	41	12.37 ± 2.5; CL, CP	COHIP, children and parents, strong internal reliability	Rating parents and children	
11	Ajami (34)[a]	50/50	8–15; CLP	COHIP, children	gender, control, type-D	• Gender (emotional well-being), Age (oral symptoms)
12	Broder (42)[a]	1196	7.5–18.5; CP, CLP	COHIP, children and caregiver	Gender, Cleft type, insurance	• Surgical recommendation • Gender • Surgery • Insurance • Visibility of cleft • Type of cleft
13	Agnew (18)[a]	222	7–18; CL, CP	COHIP-SF, children and parents, strong correlation	Age; agreement; types of cleft, private insurance	• Age (socio-emotional well-being) • Type of cleft (functional well-being)
14	Aravena (35)[a]	48/96	8–15; CL, CP, CLP	COHIP, children	Control	• CLP and control (functional well-being, school environment, self-image)

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Table I: Characteristics of the studies included in the review

No	Author	Cleft/ control (N)	Age range; types of cleft	QOL instruments, informant, correlation/consensus	Determinants	Impacted domain
15	Vuletic (36)[a]	73/70	11–18; CL, CP, CLP	QLACA, children	Control, gender, age	• Relationship with parents, • Success • Society • Appearances • Function
16	Kortelainen (12)[a]	51/82	11–14; CLP	CPQ, children	control, age, gender	• Compare control (total score, functional limitations, emotional well-being, social well-being)
17	Konan (20)	140	8–15; CLA, CLP	COHIP, children and parents, no significance between parent and children rating	Age, gender, parents' reports	• Patient and parent (self-image) Cleft type (total score and functional well-being)
18	Broder (37)[a]	1200	7–18; CP, CLP	COHIP, children	Gender, age	• Surgical recommendation • Oral health • Functional well-being • Socio-emotional well-being, school/environment
19	Ward (43)[a]	75/75	8–18; CL, CP, CLP	COHIP, children and parents, no significantdifference	Age, caregiver	• Oral health, • Functional well-being • Social emotional well-being
20	Eslami (38)[a]	50	8–15; CLP	COHIP, children	Age, gender, type of cleft	• Emotional well-being on gender

[a]Reported negative influence of CL/P on QoL.

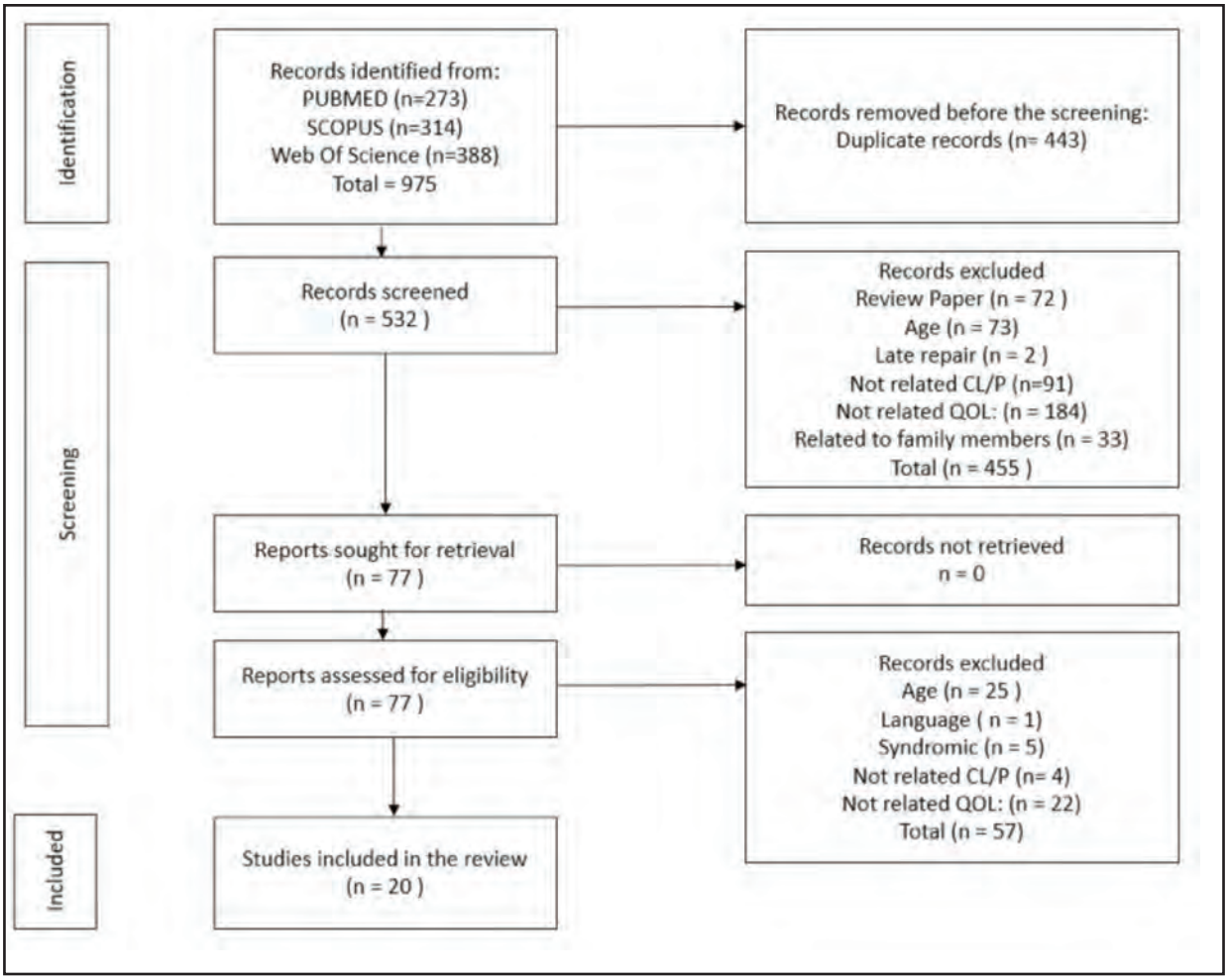

Fig. 1: Flow of the literature search and the selection process

between self-reported or parent-reported QoL of young patients with CL/P.[18-20,40-43] However, two studies reported weak correlation or statistical significance between young patients and caregivers.[13,39] These findings indicate that young patients with CL/P are capable of reporting their QoL.

QoL of Young Patients with CL/P

There was some variation in the reported QoL of young patients with CL/P in the included studies. Sixteen studies reported the negative impact of CL/P on QoL,[12,13,18,29-31,33-40,42] while four articles reported a null association between CL/P and QoL.[19,20,32,41] Three of these four studies evaluated QoL using Child Oral Health Impact Profile (COHIP) as their instrument and reported an overall COHIP score of >100 among young patients with CL/P, indicating good QoL.[19,20 41]

Nine studies compared the QoL between young patients with CL/P with unaffected control or peer groups,[12,30,31,33-36, 43,44] of which six reported statistically significant differences in the overall QoL score of young patients with CL/P compared to their peers.[12,30,31,33,36,43] As expected, young patients with CL/P had lower QoL scores than unaffected peers even though different instruments were used to evaluate QoL, such as COHIP, Child-Oral Impacts in Daily Performance (Child-OIDP), CPQ and QLACA.

When looking at specific QoL domains, young patients with CL/P and peers show statistically significant ($p<0.001$) differences in functional, social-emotional well-being and school environment.[33,43] Aleksieva[31] reported that all domains were significantly different between young patients with CL/P and their peers (total CPQ score, social, functional, emotional) except oral symptoms. Ward[43] demonstrated a significant interaction between age and social-emotional well-being in 15 to 18 years old compared to the 8 to 14 years age group. Similarly, Aravena et al.[35] showed a statistically significant difference ($p<0.05$) in functional well-being, school environment and self-images between control and young patients with CL/P; however, the overall QoL score on COHIP was not statistically significant between the two groups.

QoL of Young Patients with CL/P by Age

Nine studies used age as a determinant in their analysis. However, since young patients is a wide age range (7–18 years) were included, we dichotomised the study participants into 7–12 years old (children) and 13–18 years old (adolescents). When the age range limit exceeded these categories' boundaries, the group was defined by the mean age.

The effect of CL/P among children and adolescents has been inconsistently reported: Five studies reported a low overall QoL score but no statistically significant difference between children and adolescents.[12,30,36,38,43] For example, Ali et al.[30] and Eslami et al.[38] reported overall COHIP scores of 87.83±20.61 and 87.27±23.49 among children and 91.42±19.25 and 96.46±28.92 among adolescents, respectively. Konan et al.[20] reported high overall COHIP scores among children and adolescents but no statistically significant between-group differences. The remaining three studies reported poorer overall QoL scores among adolescents than children.[13,18,29]

Regarding domain-specific differences, Agnew et al.[18] reported that adolescents scored lower on overall and socio-emotional domains, while Lin et al.[13] reported that adolescents scored lower on overall, functional and emotional domains. However, Oka et al.[29] observed that adolescents reported lower QoL scores in all domains (stigma, negative consequence, negative self-image, positive consequence) except the coping domain.

QoL of young patients with CL/P by gender

Most studies did not find any significant difference in the overall QoL score by gender.[12,13,18,20,29,30,32,34,36,38,41,42] However, there were significant differences in specific domains. For example, three studies reported significant differences in the emotional well-being domain.[13,34,38] In a study by Broder et al.[42], female participants had lower self-rated emotional well-being and overall COHIP scores than male participants. Furthermore, Crepaldi et al.[32] reported that females scored lower in bodily pain, vitality and mental health domains. In contrast, Nolte et al.[41] reported that females scored significantly higher (higher QoL) on functional well-being and in the school environment.

QoL of young patients with CL/P by type of cleft

Nine studies reported no significant differences in QoL between cleft types[18,29-32,38,40-42] except Lin et al.[13], who reported significant differences in overall score between cleft lip (CL), cleft palate (CP) and cleft lip and palate (CLP). However, some studies reported domain-specific differences in QoL between cleft phenotypes. Six studies reported poorer QoL of young patients with CLP but were not statistically significant compared to CL and CP.[30,31,38,40-42] In contrast, Lin et al.[13] and Crepaldi et al.[32] reported that young patients with CL had lower QoL scores than patients with CLP.

Crepaldiet al.[32] also reported that young patients with CL and CP had statistically lower scores in emotional and mental health domains than those with CLP. Similarly, Agnew et al.[18] and Nolte et al.[41] reported poor functional well-being among young patients with CLP. In contrast, Aleksieva et al.[31] reported significant differences in oral symptoms and functional restriction in young patients with CLP. These inconsistent findings may be due to the timing of receiving treatment and methodological differences, such as the distribution of cleft types between studies.[30,32] Nevertheless, some studies in this review did not analyse the types of cleft separately, which may result in bias.

DISCUSSION

This scoping review aimed to identify the impact of CL/P on the QoL of young patients. A total of 20 studies were reviewed, all of which evaluated the QoL of nonsyndromic participants aged 7–18 years with CL/P using quantitative methods. In line with previous studies,[19] oral health-related QoL was commonly used to assess the outcome of multidisciplinary cleft care. The findings from this scoping review confirm that the CL/P condition affects the overall QoL scores of young patients with CL/P compared to their typically developing peers.[12,30,31,33,36,43] These findings might be explained by the fact that young patients with CL/P have more challenges at school, such as social interaction, having to undergo cleft-related treatment and aesthetic-related concerns, compared to unaffected peers.[5,45] However, three studies that use COHIP indicated relatively positive QoL (mean score = 120–155.56) in young patients with CL/P.[19,20,41] Three studies revealed positive outcomes because multidisciplinary care received as all three studies recruited participants with CL/P attended by multidisciplinary care teams from university hospitals, which may have resulted in favourable QoL scores.

Although different instruments were used to measure QoL, these instruments have been found to demonstrate reliability and validity values.[36,46-50] The main difference between instruments is the constructs measure. For example, COHIP measures oral health, functional well-being, social-emotional, school environment and self-image. Meanwhile, the YQOL-FD evaluate stigma, negative self-image, positive consequence, negative consequence and coping. CPQ measure oral symptoms, functional limitation, emotional well-being and social well-being.

We also reviewed the QoL of young participants affected by CL/P by age, gender and cleft type. The age-specific effects of CL/P on participants' QoL were heterogeneous. Three out of nine studies that used age as a determiner reported poorer QoL among adolescents (13–18 years old) with CL/P than children (7–12 years old) with CL/P,[13,18,29] especially in social-emotional well-being. These findings may be because adolescents are more concerned regarding their facial appearances as they need to cope with the facial difference in addition to typical adolescent concerns regarding appearances.[18,51] However, five studies reported low overall scores but no significant difference in the QoL between children and adolescents.[12,30,36,38,43] In contrast, Konan et al.[20] reported a numerically high overall QoL score but no significant difference between children and adolescents. There may be at least three reasons for this finding; (1) the small age range encompassing the two groups[20,30] (2) children with CL/P were as aware of their condition and had similar experiences as adolescents,[38] or (3) the studies with inadequately powered to detect age-specific differences. For instance, studies by Lin et al.[13] and Agnew et al.[18], which reported poorer QoL among adolescents compared to children, had larger sample sizes (n > 120) compared to the five studies (n = 51–75) that found no statistical difference between children and adolescent.

Regarding gender, although there was no significant between-group difference in the overall QoL scores, significant differences in domain-specific QoL scores were

noted between males and females. For example, emotional well-being was the most affected domain in females compared to males,[13,34,37,38] in line with earlier studies indicating that females tend to be more self-conscious and place greater importance on their appearances than males.[21,52,53] Similarly, nine studies showed no significant differences in the overall QoL scores by cleft types.[18,29-32,38,40-42] We also found that the QoL of young patients with cleft lip and palate is poorer, albeit not significantly, compared to patients with cleft palate.[30,31,38,40-42] These findings are similar to an earlier review by Hunt et al.[54] that reported that the type of cleft and its severity appear to have little impact on the individual's overall psychosocial functioning. It is plausible, though, that patients with visible defects (CL or CLP) may be more dissatisfied with their appearance than those without a visible cleft defect. Accordingly, Crepaldi et al.[32] and Lin et al.[13] reported poorer QoL in patients with cleft palate than those with cleft lip and palate. One of the reasons for this discrepancy is methodological differences, such as the unequal distribution of cleft types due to the unbalanced structure of participants with CL/P.[13] Secondly, those with more complex clefts may emphasise the rehabilitative process, such as facial appearances, while those with less complex clefts may consider functional aspects, such as speech.

Overall, psychological health was the most affected QoL domain in young patients with CL/P. In addition, other QoL dimensions include functional well-being (impact on the ability to carry out a specific task, e.g., speaking clearly, chewing), social-emotional well-being (implications for peer interaction and mood states) and school environment (impact on functions associated with school environment) seems to be negatively affected in young patients with CL/P. In contrast, oral health (impact on oral symptoms, e.g., pain, spots on teeth) and physical health were the least affected QoL domains.[32] This finding is similar to those reported in earlier reviews by Herkrath et al.[22] and Hunt et al.[54], which found that emotional and functional well-being are most affected in young patients with CL/P.

A plausible explanation for poor functional well-being is that young patients with CL/P have difficulty eating or speaking due to missing or rotated teeth. They may also have problems keeping their teeth clean and most children with CL/P have an orthodontic appliance which can further contribute to functional difficulties.[30,43,55] Meanwhile, challenges dealing with societal norms and expectations regarding facial appearances and communicative skills may severely affect the emotional well-being of young patients with CL/P. Furthermore, they may be more worried or anxious, experience teasing or bullying and be concerned about how others perceive them.[18,43] The school environment is another negatively impacted domain among young patients with CL/P, as also noted by Stock and Feragen.[56] For example, patients with CL/P may have otitis media; thus, they struggle at school, need to sit at the front of the class and may require more support, such as a hearing aid.[57] In addition, young patients with CL/P miss more school days than unaffected peers due to hospital appointments for cleft-related treatment.[45]

LIMITATIONS

Although we conducted this scoping review based on the PRISMA statement and used a meticulous literature search strategy, we did not include grey literature or literature published in a non-English language, which may have inadvertently led to the exclusion of some relevant research. Also, we could not assess the impact of treatment duration or patient resilience on QoL outcomes of young patients with CL/P as these areas are poorly researched.

CONCLUSION

The current review found that most studies report poor QoL outcomes in young patients with CL/P, especially in the psychological health, functional well-being, social-emotional well-being and school environment QoL domains. While different tools were used to measure QoL, the tools were generally giving consistent results with the outcomes and caregiver ratings. While QoL outcomes between children and adolescents with CL/P are inconsistently reported, the current evidence does not indicate exacerbated QoL outcomes by gender or cleft type. More studies investigating the QoL of young patients with CL/P with a larger sample size that can be representative of the population are warranted. Additionally, future studies should consider targeted prevention measures for helping young patients in the areas of psychological health, functional well-being, social-emotional well-being and school environment domains QoL domains. Resilience towards positive adjustment and the socio-economic status of young patients with CL/P should be consider as these factors may influence QoL outcomes. The World Health Organization has highlighted that assessing socio-economic characteristics is pertinent to understanding QoL outcomes.[58-60]

CONFLICT OF INTEREST AND FUNDING

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LETTER TO EDITOR

Tenebrio molitor larva: New food applied in medicine and its restrictions

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Dear Editor,

As we know, edible insects are considered a noteworthy alternative food for humans in the future. Among them, yellow mealworm *(Tenebrio molitor)* is consumed widely in a number of countries such as Korea, Thailand, China and Mexico. In particular, *T. molitor* larva can be recommended as a food with many different types (whole, chopped or ground). In addition, it can be processed in the form of powder or freeze-dried yellow mealworms. *T. molitor* larva is also used as an ingredient in different food products such as snacks, biscuits, pasta-based dishes. In fact, this natural material is a good source of energy for human and is rich in nutritional value, contains high protein content and provides essential amino acids for humans. The previous study revealed that *T. molitor* larva contains vitamins (B2, B5, and B12), minerals (Cu, Fe, Mg, Mn, Na and Zn), and phenolic compounds.[1] Based on the issues mentioned above, this is a food that could replace the other, more traditional foods (beef, pork, and chicken). However, in Vietnam and other countries, customers are not very interested in this food and consider insect eating to being culturally unacceptable and disgusting. Insect eating also incurs the risk of allergies for humans.

One of the most exciting things about *T. molitor* is that it can be targeted in the pharmaceutical and medical fields. In Indonesia, *T. molitor* is used as a drug to decrease blood sugar levels, while Samsul et al. also reported that *T. molitor* powder is a potential drug to prevent diabetes.[2] Moreover, there is a lot of evidence showing that *T. molitor* possesses anti-Alzheimer's disease, anti-obesity, anti-osteoporosis, anti-oxidation and anti-inflammation activities. One of the newest findings of the effects of *T. molitor* in 2020 is that the defatted *T. molitor* larva fermentation extract ameliorates steatosis, inflammation and intestinal microflora in chronic alcohol-fed rats. In particular, it can prevent alcohol-induced hepatocellular damage.[3] Based on the evidences mentioned above, they pointed out that the pharmacological potential of *T. molitor* larva is extremely large. So, it is necessary to research this material deeply in the future.

In general, all experiments were conducted *in vitro* as clinical practices had not yet been performed. Almost all of these studies stated that *T. molitor* could be considered a functional food ingredient or food supplement for the treatment of human diseases. However, sensory evaluation is unacceptable for the majority of consumers; in my opinion, there are many disadvantages to the application of *T. molitor* in the medical field which must be resolved, such as microbial contamination (microbes therein, including pathogens), parasites, antibiotic use, pesticides, toxins and allergens. These issues are a huge challenge for the medical field, which explains why the products from *T. molitor* (oil, extract, etc.) are not used for in vivo experiments in humans. Although there are safety concerns surrounding *T. molitor*, until now, most of the countries have not had any regulations or laws to manage the quality of *T. molitor* "from farm to table" or "from farm to medicine". Therefore, we must establish specific regulation in each country. Moreover, the customers have to be tolerant and acceptable of new nutritious foods developed as a medicine to prevent disease. Based on that, I hope that products that originate from *T. molitor* will become popular and provide greater benefits for human health. In addition, new medical effects remain to be discovered.

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LETTER TO EDITOR

Discrepancy between clinical presentation and cerebral imaging requires further diagnostic effort

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We read with interest the article by Mabel et al. about a 62-year-old male who suddenly developed right-sided facial weakness, dysarthria, vertigo, blurred vision and right-sided hemiparesis.[1] Despite this presentation, the patient was surprisingly diagnosed as Bell's palsy initially.[1] Magnetic resonance imaging (MRI) revealed a pontine ischaemic stroke.[1] It was concluded that "a thorough neurological examination and good clinical correlation with the patient's history and physical findings, coupled with the use of facial nerve anatomical knowledge and early employment of MRI, are imperative in clinching the diagnosis.[1] The study is attractive but raises concerns that should be discussed.

We disagree with the notion that the index patient had "isolated" facial weakness respectively Bell's palsy. In addition to facial palsy, the patient had dysarthria, blurred vision, vertigo and right-sided hemiparesis.

Arguments for ischaemic stroke and against Bell's palsy in the index patient are that facial weakness had an acute onset, that the patient had dysarthria in addition to facial weakness, that the cardiovascular risk profile was positive for diabetes, hyperlipidaemia and arterial hypertension, that blood pressure was increased to 192/119 mmHg on admission, and that the patient had developed right-sided hemiparesis for 2 days. In view of these facts, it is surprising that isolated facial weakness, respectively, Bell's palsy was initially considered in the index patient.

There is a discrepancy between the unilateral clinical presentation and the central location of the pontine lesion as presented in Figure 2. The central pontine lesion does not explain right-sided facial weakness and right-sided hemiparesis.

According to the clinical exam right-sided facial weakness was of the peripheral type. Since lesions of the facial nucleus also present with the peripheral type of facial weakness, it is crucial to rule out a central cause in patients with a cardiovascular risk profile as in the index patient.

Missing is an explanation of blurred vision. The MRI findings do not explain blurring. We should be told for how long blurring persisted and if this was due to arterial hypertension or diabetic retinopathy. Missing is the information about the HbA1c value. Missing are the results of funduscopy.

Missing is the exact course of the clinical manifestations. We should be informed about onset and end of each of clinical presentations, facial weakness, dysarthria, vertigo, blurring and right-sided hemiparesis.

Missing is the information whether the patient was SARS-CoV-2 negative or positive on admission. Missing is a follow-up MRI to assess if the central pontine lesion persisted or resolved.

The discrepancy between dysarthria and the statement that except for the facial nerve all other cranial nerves were intact should be solved. Of particular interest is if there were any sensory disturbances, hypogeusia, or hearing impairment. Since the patient had dysarthria, involvement of the 9th and 10th cranial nerve needs to be ruled out.

Overall, the interesting study has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Since cerebral imaging does not explain the clinical presentation, alternative causes should be considered.

Reply by the authors

We take note your interest in our article. In response to the first argument on the index patient having an "isolated" facial palsy is that despite the patient mentioning he had other peripheral symptoms such as dysarthria, some right sided hemiparesis, vertigo and blurring of vision – none of these symptoms in which he could provide details on onset, duration and severity as the author has rightly noticed. Our argument for that is stated in paragraph 4 of discussion.

All patients hospitalised during the COVID-19 pandemic would have automatically been screened at the admissions department as a standard precaution and procedure in all Malaysian hospitals. Only those who are COVID-19-negative are allowed admission.

The blurring of vision could have been part of the old lacunar infarct (as explained in paragraph 4 discussion) or diabetic retinopathy or arterial hypertension for which he was referred to the ophthalmology team for routine screening of all diabetic patients as per the Malaysia Health system protocol.

A follow-up MRI was performed as clearly stated in the last paragraph of the case report section – no new changes comparatively to the initial MRI.

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This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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