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Original Articles

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Exploring the role of quantitative electroencephalography in ischaemic stroke through spectral and topographic mapping

Kok Leong Liew, MMed[1], Juen Kiem Tan, MMed[1,2], Ching Soong Khoo, FRCP[1,2], Kai Yi Ng, BCS[3], Wilbert Chong, BCS[3], Yuet Teng Lew, BCS[3], Chee-Ming Ting, PhD[3], Hernando Ombao, PhD[4], Nursyazwana Zolkafli, MLT[1,2], Zhen Yang Lee, MD[1], Hui Jan Tan, FRCP[1,2]

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ABSTRACT

Introduction: Stroke is a major cause of morbidity and mortality worldwide. While electroencephalography (EEG) offers valuable data on post-stroke brain activity, qualitative EEG assessments may be misinterpreted. Therefore, we examined the potential of quantitative EEG (qEEG) to identify key band frequencies that could serve as potential electrophysiological biomarkers in stroke patients.

Materials and Methods: A single-centre case-control study was conducted in which patients admitted with stroke and healthy controls were recruited with consent. EEG was performed within 48 hours of admission for stroke patients and during outpatient assessments for controls. The EEG signals were pre-processed, analysed for spectral power using MATLAB, and plotted as topoplots.

Results: A total of 194 participants were included and equally divided into patients with ischemic stroke and controls. The mean age of our study cohort was 55.11 years (SD±13.12), with a median National Institute of Health Stroke Scale (NIHSS) score of 6 (IQR 4-6) and lacunar stroke was the most common subtype (49.5%). Spectral analysis, with subsequent topographic brain mapping, highlighted clustering of important channels within the beta, alpha, and gamma bands.

Conclusion: qEEG analysis identified significant band frequencies of interest in post-stroke patients, suggesting a role as a diagnostic and prognostic tool. Topographic brain mapping provides a precise representation that can guide interventions and rehabilitation strategies. Future research should explore the use of machine learning for stroke detection and provide individualized treatment.

KEYWORDS:
Quantitative EEG, qEEG, stroke, spectral EEG, topography

INTRODUCTION

Stroke is a heterogeneous disease that is characterized by various vascular, hemodynamic, and systemic abnormalities. It represents the second-leading cause of death and the third-leading cause of disability worldwide, according to the 2017 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD).[1] Structural brain lesions caused by stroke disrupt brain activity and reorganize functional connectivity, both locally and remotely from the affected site.[2] Electroencephalogram (EEG) enables non-invasive and continuous assessment of brain activity, providing qualitative or quantitative analysis of brain activity following a stroke.[3] Despite the current neurodiagnostic assessment of stroke with brain and neurovascular imaging, EEG may offer the advantage of assessing neural function and electrophysiological activity in real-time. Numerous studies have been published regarding the role of EEG in early diagnosis, outcome prediction, clinical management, seizure detection, and prognosis of stroke.[4,5]

Both qualitative and quantitative EEG (qEEG) provides valuable insights into brain activity following a stroke. In qualitative assessment, EEG patterns are divided into five main frequency bands: delta (0.5- 4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz). However, EEG data may be fraught with misinterpretation and inter-rater variability, resulting in erroneous conclusions.[6] Although sparsely used, EEG spectral analysis quantifies the amount of rhythmic activity of different frequencies to objectively measure the power of specific frequency bands and their spatial distribution. qEEG analysis provides well-defined features from EEG data, such as spectral power (through topological distribution on the scalp surface) and coherence (as a metric of association between channels).[7,8] Commonly used indices to express relative power in qEEG include the relative delta power (RDP) at 1–3 Hz, delta/alpha power ratio (DAR), and delta + theta/alpha + beta power ratio (DTABR)[9] and the brain symmetry index (BSI), which is a visual interpretation that quantifies ischemic damage over each hemisphere with good reproducibility.[10,11] These indices have been used to investigate the associations between spectral EEGs and outcomes (such as stroke severity) following stroke.[12]

Each channel and its corresponding dominant band power may indicate variations in deficit manifestation or correlate with stroke severity. For example, band power, such as heightened beta band over the occipital region and alpha activity, are generally linked to visual performance and certain forms of attention, respectively. In this regard, the identification of the commonly affected band frequencies

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may guide supportive therapy in the future. Therefore, this study aimed to identify the potential electrophysiological biomarkers in stroke patients based on the EEG spectral content. Specifically, the observed EEG band power differences between stroke patients and those without stroke, in addition to identifying the brain regions and frequency bands that expressed the largest discrepancy between both groups.

MATERIALS AND METHODS

Study design

This single-centre case-control study was conducted in Hospital Canselor Tuanku Muhriz, the National University of Malaysia, Kuala Lumpur, Malaysia, from October 2021 to May 2023 with the approval from the local Ethics and Research Board (FF-2021-436). Patients admitted with a diagnosis of ischaemic stroke were recruited using convenience sampling. Written informed consent was obtained from all participants prior to recruitment. The inclusion criteria were those age ≥ 18 years, hospitalized with a diagnosis of ischemic stroke according to the Oxfordshire classification within 14 days of admission. Exclusion criteria were stroke mimics, such as overt infections or metabolic derangements, transient ischemic attack, neurodegenerative diseases, delirium, traumatic brain injury, previous history of neurosurgery, underlying psychiatric disorders, epilepsy, and brain tumours. The control group consisted of an equal number of participants but was not completely age- and sex-matched, in view of the difficulty in acquiring adequate participants. The participants for the control group were healthy patients receiving outpatient treatment without prior episodes of stroke or a history of epilepsy.

Clinicopathological information of each participant was collected using a data collection sheet and included sociodemographic information (e.g., age and sex), clinical history, type of stroke, risk factors, and stroke severity. To quantify the severity of stroke, we used the National Institute of Health Stroke Scale (NIHSS), a quantitative assessment tool to measure deficits following a stroke that can be completed within ten minutes. It is a fifteen-item examination with a rating of three to five per item and serves as a quantitative assessment tool to measure deficits following stroke, with a total score ranging from 0 to 42. The severity can then be clinically stratified as mild (1 - 4), moderate (5 - 15), severe (16 - 24) or very severe (≥25).[13,14] It has good interrater reliability (kappa = 0.69) and test-retest reliability (kappa = 0.66 - 0.77).[15]

An EEG was recorded within 48 hours of admission for all participants in the case group and on outpatient assessment for the control group by two neurodiagnostic technologists. The EEGs were recorded using the Nicolet One Extension (V32 Amplifier) with a sampling rate of 500 Hz according to the international 10–20 system with a bipolar montage. 24 reusable gold electrodes were fixed over the scalp and earlobes and cleaned with Nuprep. The abbreviations on the EEG are as follows: Fp, frontopolar; C, central; F, frontal; T-temporal; P, parietal; and O, occipital. Each recording lasted for a minimum of 30 minutes.

EEG Analysis

The raw EEG data obtained were exported to MATLAB 2020a, a programming software for preprocessing and spectral analysis. The raw EEG data underwent data preprocessing to filter out noise and myogenic artefacts. The EEG signals were filtered from power-line interference (PLI) using a notch filter at 50 Hz and then bandpass-filtered at a low cutoff frequency (0.5 Hz) and a high cutoff frequency (70 Hz) to allow only frequencies of interest to pass for subsequent analysis. The signal of each channel was standardized to have a mean of zero and variance of 1. Average referencing was further applied by computing the average of the signals at all channels and subtracting them from the EEG signal at every channel.

Subsequently, post-processing data were used for power spectral analysis based on Fourier transform analysis. A fast Fourier transform was applied to the EEG signals of each channel. The result of the frequency analysis is expressed as the spectral power based on Fourier periodograms, that is, the squared amplitude of the fast Fourier transform of the EEG (μV2). The band-limited power spectra or band power was computed using Matlab2020a band power function for each of the five main EEG frequency bands (i.e., delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-100 Hz)) across all channels for each subject. Topolot from the EEGLAB toolbox was used to graphically visualize the frequency content of the EEG signals over the channels and pinpoint areas of interest.

Statistical Analysis

IBM SPSS Version 26 was used for the analysis of descriptive data. Categorical variables were presented as frequencies and percentages. Normality was tested using skewness and kurtosis for all continuous variables. The mean and standard deviation (SD) were for normally distributed continuous variables; however, non-parametric analysis was used when the data were not normally distributed. A paired t-test statistical analysis was performed to identify the significant difference in the EEG mean band-power differences between the stroke patient and control groups with a significant threshold set at p-value < 0.05 (uncorrected for multiple comparisons).

RESULTS

Clinicodemographic data

A total of 233 participants were screened. Eventually, a total of 194 participants (97 stroke patients and 97 controls) were recruited based on the study criteria and following informed consent. The mean age of the study population was 55.11 years (SD±13.12). One hundred participants were male (56 cases, 44 controls) and 94 were female (41 cases, 53 controls). Upon analysis of the patient group, the median NIHSS score at presentation was 6 (IQR 4-6). Almost half (49.5%) of the patients with stroke had lacunar stroke, followed by partial anterior circulation stroke (29.9%). Lacunar infarcts were the most commonly observed neuroimaging finding on computed tomography (CT) of the brain, accounting for 57.7%, with middle cerebral artery territory infarcts the 2nd most commonly encountered abnormality (32%). The EEG characteristics of 40 participants in the patient group were

normal. 57 had abnormalities in EEG recording, most notably focal slowing (34 patients). The control group had normal EEG findings in all 97 participants. The clinical characteristics of the patients are summarized in Table I.

Band power comparison over each channel
Following the sociodemographic analysis, we focused on identifying band power and channels of interest between the patient and control groups. We performed univariate sample analysis using an independent sample t-test to identify significant differences between the groups, accepting a p-value <0.05 as significant. Table II elaborates the p-values of all categories of band power and corresponding channels when comparing patients with and without stroke.

Topographic brain mapping
Subsequently, we plotted a topological map to delineate the spatial representation of data across the tested channels. Colour scales were used to display the strength of specific variables or measurements at each point to aid data visualization. The dark blue and red colours indicate values closer to 1.0 and 0.1, respectively. Figure 1 shows a topographical map of the p-values obtained by comparing the patient and control groups. To assist in visualizing the areas of interest, we projected another topoplot to highlight the areas where the p-value was significant and used different hues to signify lower p-values. This is illustrated in Figure 2a. The topographical brain mapping of p-values reveals that there are statistically significant differences in the mean band power between the patient and control groups in the alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-100 Hz) frequency bands. These differences are indicated by the red regions in the corresponding maps, where the p-values are below the common threshold of 0.05, suggesting a strong likelihood that these variations are not due to chance. In contrast, the delta (0.5-4 Hz) and theta (4-8 Hz) bands show no significant differences between the two groups, as indicated by the higher p-values (represented by blue and green regions).

Overall, these findings highlight that the most substantial and statistically significant differences in brain activity between the patient and control groups are present in the higher frequency bands (alpha, beta, and gamma), which may have important implications for understanding the underlying neurological or cognitive processes.

The analysis revealed that the important channels were predominantly clustered in the band power belonging to alpha, beta and gamma bands. We calculated the difference in the mean of all significant band powers by subtracting the mean of the control from the mean of the sample data. This was performed to quantify the average disparity or variation between the groups. A positive difference indicates higher values in the sample, whereas a negative difference indicates lower values. Table III illustrates the differences in mean band power between the two groups. The non-significant band powers were slashed to avoid confusion. Figure 2b depicts the findings in Table III in the form of a topoplot to aid visualization. The regions identified in Figure 1 as having significant p-values are the same regions in Figure 2b where there are substantial differences in mean band power. When these figures are considered together, they provide a more comprehensive view. The significant regions in Figure 1 are either positive or negative in Figure 2b, indicating whether the patient group has an increase (blue regions) or decrease (red regions) in band power. Merging these insights gives a full picture of where and how the patient group's brain activity differs from that of the control group, both in terms of significance and direction (increase or decrease). This combined analysis helps to clarify not only the presence of significant differences but also the nature of these differences in brain activity between the patient and control groups.

DISCUSSION

Demographic data
Our study population consisted mainly of patients with lacunar stroke. This could explain the lower NIHSS score in our cohort, with a mean of six (moderate severity). This is comparable to most studies in the region, with data from Asian countries suggesting a higher prevalence of small vessel disease subtypes, particularly in Southeast Asia.[16,17] Studies from Thailand and Malaysia have suggested a high percentage of intracranial atherosclerosis (approximately 52.6% and 28%, respectively), although the current trend shows a decline.[18,19]

Difference in EEG band power between patient and control group
Qualitative analysis of EEG in our cohort showed epileptiform changes and focal and diffuse slowing. This finding concurred with the slowing of background activity, background asymmetry, and periodic discharges frequently observed in post-stroke patients and those with poor functional outcomes.[20] A study by Giaquinto et al. demonstrated a higher degree of slowing over the affected hemisphere, which may improve or outlast the clinical improvement.[21] Therefore, they suggested a possible role of EEG in monitoring neural repair and guiding rehabilitation. Focal slowing accounted for 35.1% of the EEG changes observed in our cohort with stroke. This finding is similar to that of studies showing focal and diffuse slowing as the predominant abnormality observed post-stroke. These changes are associated with a lower risk of post-stroke seizures than abnormalities such as periodic lateralized discharges.[22] However, there is a link between the slowing of EEG background and cognitive impairment, as reported by Moretti et al. in their cohort with greater cerebrovascular damage.[23] Generalized slowing was also associated with poorer clinical outcomes.[24]

We observed a significant association between alpha, beta, and gamma band powers when comparing both groups of patients. This is in line with studies demonstrating increased synchronization and lower frequency of alpha oscillations, increased high beta (21-30 Hz) compared to low beta (13-20 Hz) bands centrally, elevation of beta oscillatory power, and disruption of gamma oscillatory patterns following an acute stroke.[25-27] Less efficient and more modular networks were observed, particularly in the beta and gamma bands, which explains the association in our study.[27] However, these changes evolve during recovery, with alpha desynchronization observed weeks after an acute stroke. A greater degree of event-related desynchrony over the affected

Table I: Clinical characteristics of patient group

Clinical characteristics	n = 97 (%)
National Institute of Health Scale Stroke	
Mild (1-4)	43 (44.3)
Moderate (5-15)	33 (34.0)
Severe (16-24)	15 (15.5)
Very severe (≥25).	6 (6.2)
Stroke Types:	
Total Anterior Circulation Infarct (TACI)	9 (9.3)
Partial Anterior Circulation Infarct (PACI)	29 (29.9)
Lacunar Infarct (LACI)	48 (49.5)
Posterior Circulation Infarct (POCI)	11 (11.3)
Hemispheric Involvement:	
Total Anterior Circulation Infarct (TACI)	L 4 (4.1)
	R 5 (5.1)
Partial Anterior Circulation Infarct (PACI)	L 16 (16.5)
	R 13 (13.4)
Lacunar Infarct (LACI)	L 26 (26.8)
	R 22 (22.7)
Posterior Circulation Infarct (POCI)	L 4 (4.1)
	R 3 (3.1)
Neuroimaging Characteristics:	
Middle Cerebral Artery (MCA)	31 (32.0)
Anterior Cerebral Artery (ACA)	2 (2.1)
Posterior Cerebral Artery (PCA)	5 (5.2)
Lacunar Stroke	56 (57.7)
Others	3 (3.1)
EEG Characteristics:	
Normal	40 (41.2)
Focal slowing	34 (35.1)
Diffuse slowing	18 (18.6)
Epileptiform	5 (5.2)

Note:
SD- Standard Deviation
IQR - Interquartile Range
R- Right
L- Left

side correlated with a higher degree of clinical improvement.[28] The increase in beta activity over time at the central region contralateral to the affected side correlated with good functional motor recovery than if the increase is seen in the affected side suggesting a role in neuroplasticity in functional recovery.[26]

Several studies have reported a high incidence of focal or diffuse slowing in patients with acute strokes.[29] Our analysis did not reveal a significant difference in delta and theta band power, but this could be explained by the type of stroke in our cohort. Only one-third of the patients in our cohort had middle cerebral artery territory infarcts, whereas the majority had lacunar infarcts. Delta activity is strongly correlated with regional cerebral blood flow; therefore, it is more prominent in middle cerebral and internal carotid artery territory strokes.[3]

Future applications

Identifying specific band powers of interest may be essential for post-stroke rehabilitation. Different band powers are linked to different motor and non-motor functions. Beta oscillations have been associated with movement production, whereas gamma rhythms are amplified during cognitive processes.[30,31] These may be appreciated predominantly in different areas of the cortex. Numerous non-invasive neuromodulation techniques have been investigated, including transcranial magnetic stimulation, transcranial electrical stimulation, and transcranial focused ultrasound stimulation. Although the frequency and dosing for each indication may vary among studies, there is a need for accurate identification of the stimulation site, which could be aided by qEEG analysis.[32] This would affect the overall efficacy of treatment.

The use of topographical brain mapping would further improve the identification of sites for intervention, based on the significance and area involved. This can be achieved with readily available software, as we have demonstrated that it can be integrated into the device used for neurorehabilitation. Another application is the use of qEEG in brain-computer interfaces, which could be used as a driving command for rehabilitation systems and exoskeletons or prostheses to improve overall functions. Raw

Table II: P-values of t-test of mean EEG band power differences between patient and control groups for each channel and each frequency band

Channel	Delta	Theta	Alpha	Beta	Gamma
Fp1	0.617	0.8409	0.22806	0.081487	0.25405
Fp2	0.79612	0.91956	0.14324	0.10257	0.49415
F3	0.62613	0.41135	0.059265	0.013185*	0.033681*
F4	0.41968	0.83696	0.43514	0.19042	0.37654
C3	0.14908	0.15116	0.035899*	0.032296*	0.14962
C4	0.91018	0.83967	0.058827	0.046295*	0.12752
P3	0.44359	0.23648	0.019362*	0.051704	0.1233
P4	0.69974	0.78972	0.060861	0.24813	0.57825
O1	0.33701	0.59323	0.13111	0.074822	0.17522
O2	0.18071	0.3145	0.065623	0.074138	0.38033
F7	0.20321	0.36221	0.067397	0.012234*	0.029692*
F8	0.84855	0.89918	0.13684	0.038713*	0.10717
T7	0.60718	0.86628	0.79646	0.031618*	0.034612
T8	0.053969	0.085305	0.49281	0.43906	0.24726
P7	0.59615	0.34481	0.014077*	0.047394*	0.12412
P8	0.23651	0.75712	0.56663	0.11144	0.095838
Fz	0.45013	0.22602	0.03721*	0.18748	0.77028
Cz	0.81084	0.41017	0.047992*	0.022214*	0.070232
Pz	0.14433	0.1715	0.044783*	0.006018*	0.021365*

*p-value significant at <0.05
Fp: frontopolar, C: central, F: frontal, T: temporal, P: parietal, O: occipital

Table III: Difference in mean band power between patient and control groups for each channel and each frequency band

Channel	Delta	Theta	Alpha	Beta	Gamma
Fp1	0.00011	0.000015678	-0.00012	-0.00013	-0.00007185
Fp2	0.000066032	-0.000008498	-0.00015	-0.00015	-0.00004572
F3	-0.00022	-0.00018	-0.00042	**-0.00073***	**-0.00063***
F4	0.001673	-0.00015	-0.00065	-0.0015	-0.00094
C3	-0.00055	-0.00028	**-0.00054***	**-0.00061***	-0.00044
C4	-0.00022	-0.00016	-0.00187	**-0.00256***	-0.00142
P3	-0.0002	-0.00013	**-0.00041***	-0.00022	-0.00009173
P4	-0.00019	-0.000064653	-0.00064	-0.00028	0.000082449
O1	0.000151	-0.000032812	-0.00012	-0.0001	-0.00005957
O2	0.000226	-0.0001	-0.00025	-0.00013	-0.00003550
F7	-0.00027	-0.000070885	-0.00018	**-0.00022***	**-0.00025***
F8	0.000074323	-0.000020166	-0.00025	**-0.00031***	-0.00027
T7	-0.00009208	0.0000087818	-0.00002056	**-0.00019***	**-0.00026***
T8	0.000504	0.000245	0.000121	-0.00012	-0.0002
P7	0.00006443	-0.000059889	**-0.00018***	**-0.00013**	-0.00007399
P8	0.000216	0.000032279	-0.00012	-0.00017	-0.00013
Fz	-0.00008685	-0.000061502	**-0.00012***	-0.00009225	-0.00001722
Cz	0.000031926	-0.000055273	**-0.00017***	**-0.00017***	-0.00009517
Pz	-0.00249	-0.00131	**-0.0017***	**-0.0025***	**-0.00126***

*difference in mean of significant band power and channels in both groups
Fp: frontopolar, C: central, F: frontal, T: temporal, P: parietal, O: occipital

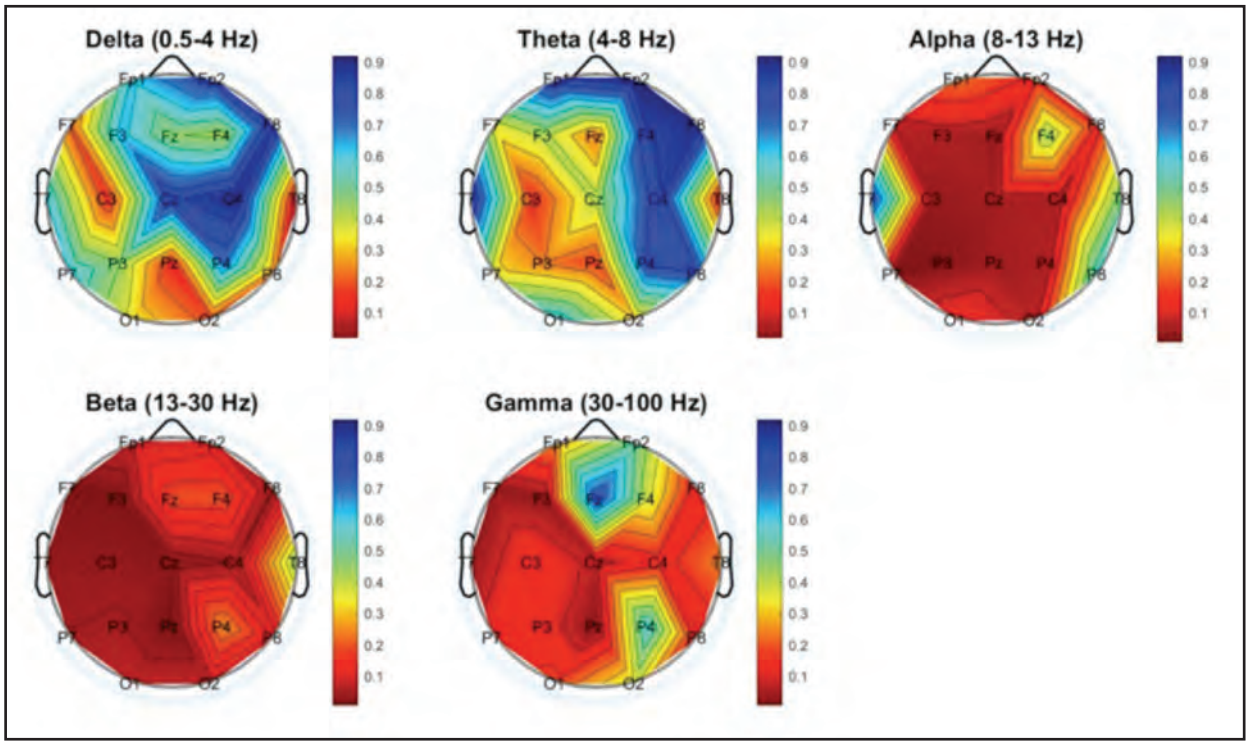

Fig. 1: Topographical brain mapping of p-values obtained from t-test of the mean band power difference between patient and control group. The coloured scale indicates the p-value; red being the lowest p-value

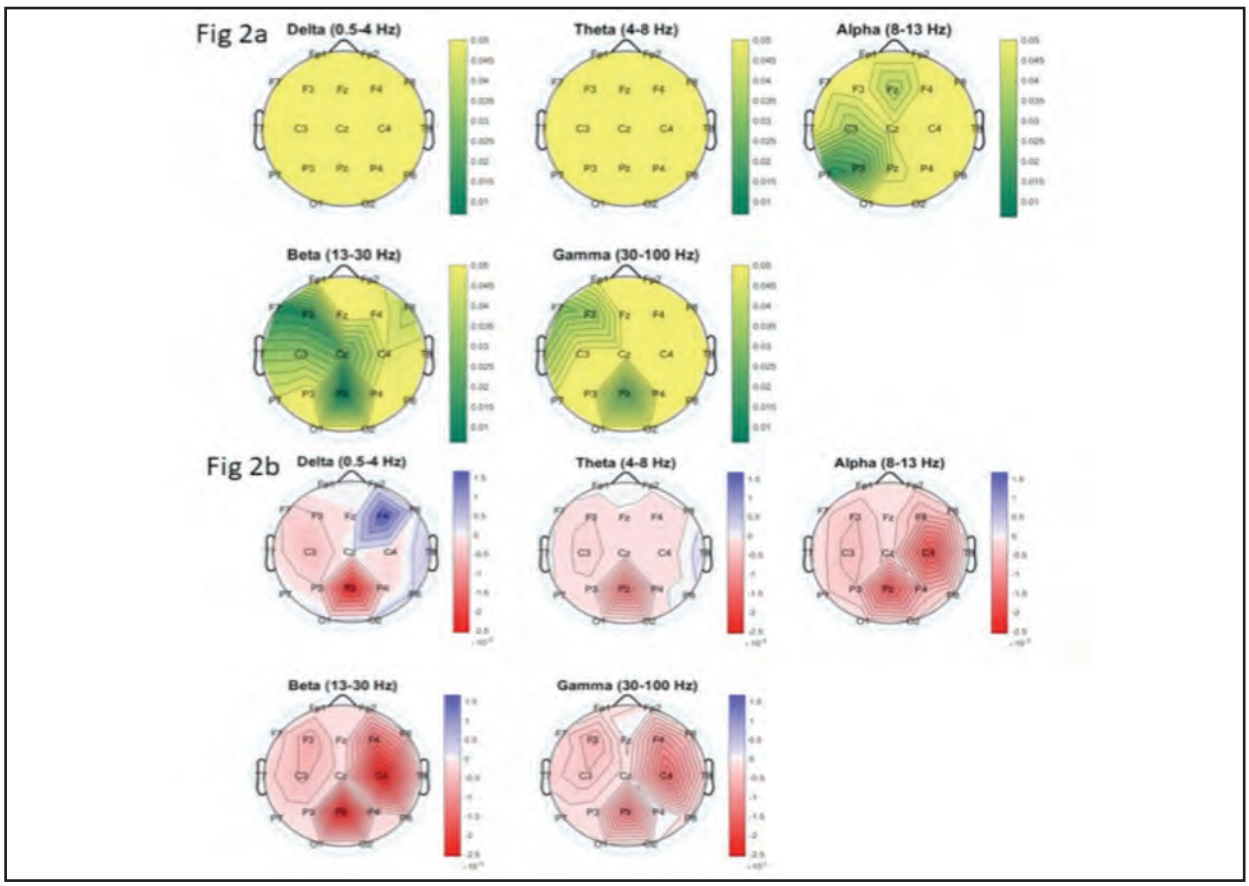

Fig. 2: a) Topographical brain mapping demonstrates only significant p-values ($p<0.05$) when comparing band power of patient and control group. A darker hue of green indicates a lower p-value.
b) Topographical brain mapping of the difference in mean band power for each channel and frequency between patient and control groups. The positive values represent an increase in mean band power (displayed in blue) in patient group relative to the control group, while the negative values signify decrease in mean band power in patient group relative to control group (displayed in red).

EEG data can be converted to produce movements in actuators to allow gross and fine motor actions, which may require electromyography as an adjunct.[33,34]

Moving forward, we plan to improve the graphical user interface to make the program more user-friendly so that data can be extracted and utilized by neurodiagnostic technicians and rehabilitative support staff. We intend to explore the use of machine learning, such as a Support Vector Machine, to investigate whether it is possible to use band power variations to detect acute stroke, especially in the setting of stroke mimics or a history of stroke. To improve the accuracy, we aim to recruit more participants once adjustments have been made to the software algorithms.

One limitation is that our cohort included all stroke subtypes, regardless of the etiology, type of therapy administered, and area involved. This may result in EEG changes following interventions such as mechanical thrombectomy or thrombolysis. The band power significance may be altered because of the different areas of the stroke. However, we could not standardize the side or territory involved because of the limited number of participants. In addition, the median NIHSS score in our study is on the lower end and mainly lacunar type stroke which would produce localized abnormalities. Therefore, increasing the number of EEG channels studied may increase the yield of the study.

CONCLUSION

Quantitative EEG is a viable tool to identify band frequencies of interest in post-stroke patients. Accompanied by a topograph, a more precise graphical representation of the areas involved may guide further intervention and rehabilitation. We believe that the data obtained from qEEG would be important in software programming to individualize treatment in the future and to gather data objectively when searching for the validity of biomarkers in stroke research.

DECLARATION OF CONFLICT OF INTEREST

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

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CONTRIBUTIONS

Kok Leong Liew (KL): study concept and design, acquisition of data, analysis and interpretation, drafting the manuscript. Juen Kiem Tan (JT), Ching Soong Khoo (CSK): acquisition of data, analysis and interpretation, and drafting the manuscript. Kai Yi Ng (KN), Wilbert Chong (WC), Yuet Teng Lew (YL), Chee-Ming Ting (CT): acquisition of data, data analysis and interpretation, revised manuscript and statistical analyses. Hernando Ombao (HO): data analysis and interpretation, revised manuscript, and statistical analyses. Nursyazwana Zolkafli (NZ): acquisition of data, analysis and interpretation, and revised manuscript Zhen Yang Lee (ZY Lee): acquisition of data, analysis and interpretation. Hui Jan Tan (HT): Study concept and design, methodology, funding acquisition, data acquisition, drafting and revised manuscript, and study supervision. All authors read and approved the final manuscript.

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Determinants of unsuccessful treatment outcomes among relapse tuberculosis patients in selangor registered in National Tuberculosis Registry from year 2015 – 2019

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ABSTRACT

Introduction: Despite the availability of highly effective treatment for tuberculosis (TB), patients with TB may experience a relapse, which can be either a result of the disease reactivating or a new episode induced by reinfection. In Malaysia, there has been a noticeable rise in relapse TB cases, with a substantial rate of unsuccessful treatment outcomes among this population. This study seeks to examine the trends of unsuccessful treatment outcomes in relapse TB patients and explore how factors such as sociodemographic characteristics, TB disease profile, TB treatment profile, and comorbidities contribute to the outcomes.

Materials and Methods: This is a retrospective cohort study utilising secondary data from the National Tuberculosis Registry (NTBR). The study was conducted in Selangor among relapsed TB patients who were registered in NTBR from 1 January 2015 to 31 December 2019. TB disease profile, TB treatment profile, comorbidities, and sociodemographic data were examined. The determinants of unsuccessful treatment outcomes among relapsed TB patients were identified using multiple (binary) logistic regression analyses.

Results: 896 patients who experienced relapsed tuberculosis were included in this study. 32.25% were reported to have unsuccessful treatment outcomes. Multiple (binary) logistic regression revealed that the absence of sputum smear examination at 5 months and beyond was a determinant of unsuccessful treatment outcome (AOR 1.70 (95% CI: 1.19, 2.44). Additionally, being treated in government facilities, such as government hospitals and government primary health clinics, was a protective factor (AOR 0.06 (95% CI: 0.03, 0.15) and AOR 0.02 (95% CI: 0.01, 0.04), respectively.

Conclusion: The high proportion of unsuccessful treatment outcomes among relapse TB patients stresses the importance of adherence to routine sputum monitoring and public-private partnerships.

KEYWORDS:
Tuberculosis, Relapse, Recurrent, Retreatment

INTRODUCTION

Adapting the World Health Organization (WHO) definition and reporting framework for tuberculosis (TB) in 2013[1], Malaysia uses the term "relapse" to describe all TB recurrences during programmatic assessments. The term "relapse" refers to patients who had previously received treatment for TB and were declared cured or completed treatment during their most recent treatment and are now being diagnosed with a recurrence episode of tuberculosis. It can be either due to a true relapse from reactivation of the disease or a new episode of TB caused by reinfection.[2] Many studies used the term "recurrent TB" to describe previously treated patients who had successfully treated and later presently had active TB.[3,4] The WHO standard 6-month regimen is recognized as highly effective in drug-susceptible TB. However, even with effective treatment, patients can still develop a relapse TB.[5,6] Approximately 2-4% of individuals who get the treatment in trial settings encounter a relapse and need retreatment over a span of 2 years.[7] However, a higher proportion may be seen under programmatic conditions in high-burden regions.[8,9] In 2015, the WHO estimated that 430,000 individuals who had previously received treatment for tuberculosis were diagnosed with relapse TB. This accounted for around 7% of all reported cases of TB.[10]

In Malaysia, an increasing trend in retreatment cases was reported between 2012 and 2015, from 6.4% to 6.7%, 7.3%, and 7.4%, respectively. In 2015, the highest proportion contributing to retreatment were relapse cases (4.71%), followed by treatment after default cases (2.33%) and treatment after failure cases (0.36%).[2] Rising relapse TB cases will contribute to an increasing number of TB incidences, and this vulnerable group of patients tends to have unsuccessful treatment outcomes. Unsuccessful treatment outcomes can be defined as treatment failure, loss to follow-up and death.[1,2] Relapse TB patients are more inclined to suffer higher mortality, loss to follow-up and treatment failure compared to those with the first episode of TB.[3,11,12]

Selangor is the most populated and multi-ethnic state in Malaysia and recorded the highest number of TB cases in 2018 with 5,071 cases and from 2019 to 2021, contributed up to 20% of total TB mortality in Malaysia.[13-15] According to the National TB Registry data for 2019, only 70% of relapsed TB patients in Selangor had achieved treatment success.[16]

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Among risk factors contributing to unsuccessful treatment outcome among relapsed TB patients reported in previous literatures worldwide were male, positive sputum smear after 3 months of treatment, alcohol abuse, inadequate adherence to treatment, substance abuse, being current smoker, homelessness, staying in rural areas, drug resistant TB, smear positive pulmonary TB, HIV co-infection, working while on treatment and lack of family support. [11,17–20]

Despite efforts made in the implementation of the TB control program and the availability of effective treatment, Malaysia is facing a challenge and has yet to achieve the target of 90% successful TB treatment set by the WHO. The proportion of successful treatment achieved is 81.5% for new cases and 77.1% for relapse TB cases.[21] Numerous studies were conducted in Malaysia on unsuccessful TB treatment outcomes, but insufficient attention was given to relapse TB. Previous studies included overall and mixed categories of TB cases (combination of new cases, relapse cases, as well as return after loss to follow-up cases), however none of the previous studies focused specifically on relapse TB and how determinants such as sociodemographic, TB disease profile, TB treatment profile and comorbidities contribute to unfavourable treatment outcome. Relapse TB poses a significant threat to the emergence of drug resistance and its secondary spread in the community.[22,23] Therefore, this study would like to investigate the determinants of unsuccessful treatment outcomes among relapsed TB patients to highlight various areas to focus on in tuberculosis control efforts.

MATERIALS AND METHODS

Study Design

This study is a retrospective cohort study utilizing secondary data acquired from the National Tuberculosis Registry (NTBR).

Locations and Study Population

The study was carried out in Selangor among relapsed TB patients who were registered in NTBR from 1 January 2015 to 31 December 2019.

Data Collection and Sampling Strategy

The inclusion criteria encompassed all individuals aged 18 years or older who had been diagnosed with relapse TB. NTBR is an online tuberculosis registry utilized by the Ministry of Health Malaysia to oversee the national tuberculosis control program. TB case notification, investigation, and treatment is documented in the registry. The exclusion criteria were patients with insufficient data on treatment outcome, patients initially registered as TB cases but subsequently diagnosed with other conditions, patients whose treatment outcome remained incomplete (e.g., those still undergoing treatment with unknown outcome), and patients with Multidrug-resistant tuberculosis (MDR-TB). As per WHO reporting system, it is recommended to separate and exclude cases with MDR-TB from the general TB main cohort when calculating treatment outcomes.[1] This is because the criteria for determining treatment outcome for MDR-TB cases are different. The study included all patients who met the eligibility criteria by using universal sampling.

Sample Size

The sample size was determined using OpenEpi for a single population proportion based on the largest sample size identified in a study by Tok et al.[21] which reported a proportion of 22.9% for unsuccessful TB treatment outcomes in relapsed TB patients. With a 95% confidence interval (CI) and 5% desired precision, the minimum sample size required for this study was 354 after an estimated 30% was added to the final sample size estimates to account for potential incomplete data. Nevertheless, this study included all relapse TB patients registered in the Selangor NTBR database between 2015 and 2019, resulting in a total sample size of 896.

Operational Definition

The outcomes of TB treatment were defined and monitored during surveillance over a one-year period. The treatment outcome operational definitions employed in the study were based on the WHO definitions and reporting framework for TB, the Clinical Practice Guidelines for Management of Tuberculosis, and the Ministry of Health Malaysia National Tuberculosis Information System Manual (2018 Revision). [1,24-27] The operational definition for treatment outcome in this study was as follows:

1. Cure: A tuberculosis patient who was initially bacteriologically confirmed and had a negative smear or culture during the last month of treatment or on at least one previous occasion.
2. Completed treatment: A tuberculosis patient who has successfully completed treatment without meeting the criteria for cure or failure.
3. Treatment Failure: A TB patient whose sputum smear or culture was positive at any point during treatment, whether it was at five months or later.
4. Loss to follow-up: A TB patient who failed to initiate treatment or whose treatment was interrupted for a period of two consecutive months or more.
5. Died: A TB patient who passes away for any reason prior to or during TB treatment (all-cause mortality).

In this study, the dependent variable for this study was the treatment outcome. It was categorized as a dichotomous variable, either an unsuccessful or successful treatment. Unsuccessful treatment was defined as treatment failure, mortality, and loss of follow-up. On the other hand, successful treatment was defined as completed treatment or the cure of patients. Relapse TB patients were defined by category of TB cases and according to their history of previous cases, individuals who were previously treated for tuberculosis and were declared cured or completed their treatment but presented again and diagnosed with a new recurrent episode of tuberculosis. This recurrence can be either a true relapse or a new episode of tuberculosis caused by reinfection.

Data Analysis

All statistical analyses were performed by using Statistical Package for Social Science (SPSS) software version 29.0. Descriptive statistics were used to describe the study population's characteristics. Categorical variables were presented in frequency and percentage (%), while numerical

Table I: Sociodemographic characteristic of Relapse TB patients (n=896)

Variables	Total (n = 896) n (%) [a]	Unsuccessful TB treatment (n = 261) n (%) [b]	Successful TB treatment (n = 635) n (%) [b]
Socio-demographic			
Age (in years) [c]	43.0 (23.0)	43.0 (20.0)	42.5 (23.0)
Personal income (in RM)	350 (2000)	400 (2000)	350 (2000)
Nationality			
Non-Malaysian	40 (4.5)	10 (3.6)	30 (4.9)
Malaysian	856 (95.5)	270 (96.4)	586 (95.1)
Gender			
Female	274 (30.6)	84 (30.0)	190 (30.8)
Male	622 (69.4)	196 (70.0)	426 (69.2)
Ethnicity			
Chinese	114 (12.7)	37 (13.2)	77 (12.5)
Malay	555 (61.9)	187 (66.8)	368 (59.7)
Indian	159 (17.7)	40 (66.82)	119 (59.7)
Others	52 (8.4)	16 (5.7)	68 (7.6)
Education status			
Tertiary	170 (19.0)	58 (20.7)	112 (18.2)
Secondary	535 (59.7)	161 (57.5)	374 (60.7)
Primary	72 (8.0)	26 (9.3)	46 (7.5)
Others	119 (13.3)	35 (12.5)	84 (13.6)
Employment status			
Yes	448 (50.0)	139 (49.6)	309 (50.2)
No	448 (50.0)	141 (50.4)	307 (49.8)
Location of residence			
Rural	189 (21.1)	52 (18.6)	137 (22.2)
Urban	707 (78.9)	228 (81.4)	479 (77.8)

[a]Within total sample. [b]Within the relapse TB who had unsuccessful treatment [c]Median (IQR)

variables were expressed in mean with standard deviation (SD) or median with interquartile range (IQR) depending on the normality of the data. Then, Inferential statistics were done to determine factors associated with unsuccessful TB treatment outcomes in relapse TB patients. Simple logistic regression analysis was used to determine the association between socio-demographic, TB treatment-related, TB disease-related, and comorbidities factors with unsuccessful TB treatment outcomes in relapsed TB patients. Only variables with a p-value <0.25 in simple logistic regression or that are clinically important were selected for multiple logistic regression (binary) analysis to obtain the adjusted odds ratio (aOR). A p-value of 0.05 with a 95% confidence interval was used to indicate statistical significance in all analyses.

Ethics Approval

This study utilized secondary data and did not contain any patient-identifying information. As all cases were anonymized, informed consent was not obtained from individual patients. The Medical Research and Ethics Committee, Ministry of Health Malaysia, Faculty Ethics Review Committee, Faculty of Medicine, MARA University of Technology (UiTM) approved this study.

RESULTS

From 2015 to 2019, 1291 relapse TB cases were recorded out of 24644 TB cases in the National TB registry in Selangor. The total number of relapse TB cases included in the analyses was 896, after excluding cases with incomplete data on treatment outcomes (n: 8), cases with a change of diagnosis (n: 54), and MDR-TB (n: 38), and duplicated data (n: 284). By using a total number of relapse TB patients with complete treatment outcomes at one year of surveillance (N: 869), 32.25% of relapse TB patients had unsuccessful outcomes. The flow diagram of data extraction was summarized in Figure 1. The trends of unsuccessful outcomes among relapsed TB patients in Selangor were noted to increase from 2016 to 2019, with the highest being in 2018, which reported a 36% unsuccessful rate. (Figure 2)

Characteristics of relapses in TB patients

The sociodemographic characteristics of the study population were illustrated in Table I. The median age for overall relapse TB cases was 43 years (IQR 23). In terms of relapse TB patients with unfavourable treatment outcomes, most of them were Malaysian citizens (96.4%), the male was predominant (69.4%), 66.8% were Malays, 81.4% were from urban areas, and almost 80% had secondary, lower, and informal education.

Table II depicted clinical profiles of relapse TB patients, which combined TB disease profile, treatment profile, and comorbidities characteristics. Most patients with unsuccessful outcomes had smear-positive pulmonary TB (62.9%), follow-up sputum monitoring at 2 months noted that 3.9% still had positive smears, and 26.8% of them had no sputum examination done. For subsequent sputum monitoring at 5 months and beyond, 1.4% was noted to have positive smear, and unfortunately, 65.7% of patients had no sputum examination done at 5 months of treatment and upon treatment completion.

Table II: Clinical profile of among Relapse TB patients (n=896)

Variables	Total (n = 896) n (%) [a]	Unsuccessful TB treatment (n = 261) n (%) [b]	Successful TB (n = 635) n (%) [b]
Clinical profile			
TB case detection			
Active	38 (4.2)	13 (4.6)	25 (4.1)
Passive	858 (95.8)	267 (95.4)	591 (95.9)
Anatomical site of TB infection			
Extrapulmonary	117 (13.1)	44 (15.7)	73 (11.9)
Pulmonary	779 (86.9)	236 (84.3)	543 (88.1)
Sputum AFB at diagnosis			
Negative	300 (33.5)	98 (35.0)	202 (32.8)
Positive	582 (65.0)	176 (62.9)	406 (65.9)
Not done	14 (1.6)	6 (2.1)	8 (1.3)
Sputum AFB at 2 month			
Negative	668 (74.6)	194 (69.3)	474 (76.9)
Positive	32 (3.6)	11 (3.9)	21 (3.4)
Not done	196 (21.9)	75 (26.8)	121 (19.6)
Sputum AFB at ≥ 5 month			
Negative	388 (43.3)	92 (32.9)	296 (48.1)
Positive	11 (1.2)	4 (1.4)	7 (1.1)
Not done	497 (55.5)	184 (65.7)	313 (50.8)
Chest Radiography			
No lesion	81 (9.0)	30 (10.7)	51 (8.3)
Minimal lesion	500 (55.8)	155 (55.4)	345 (56.0)
Moderate lesion	271 (30.2)	82 (29.3)	189 (30.7)
Far advanced	31 (3.5)	8 (2.9)	23 (3.7)
Not done	13 (1.5)	5 (1.8)	8 (1.3)
Type of health facilities			
Private	53 (5.9)	47 (16.8)	6 (1.0)
Government Hospital	647 (72.2)	213 (76.1)	434 (70.5)
Government Primary Health Clinic	196 (21.9)	20 (7.1)	176 (28.6)
Treatment duration			
≥6 months	550 (61.4)	165 (58.9)	385 (62.5)
<6 months	346 (38.6)	115 (41.1)	231 (37.5)
DOTS (intensive)			
Yes	760 (84.8)	230 (82.1)	530 (86.0)
No	136 (15.2)	50 (17.9)	86 (14.0)
DOTS (Supervisor)			
Healthcare worker (HCW)	427 (47.7)	138 (49.3)	289 (46.9)
Family member	422 (47.1)	124 (44.3)	298 (48.4)
No supervisor	11 (1.2)	4 (1.4)	7 (1.1)
Others	36 (4.0)	14 (5.0)	22 (3.6)
BCG scar			
Yes	826 (92.2)	264 (94.3)	562 (91.2)
No	70 (7.8)	16 (5.7)	54 (8.8)
Smoking			
No	581 (64.8)	181 (64.6)	400 (64.9)
Yes	315 (35.2)	99 (35.4)	216 (35.1)
HIV			
No	771 (86.0)	235 (83.9)	536 (87.0)
Yes	95 (10.6)	32 (11.4)	63 (10.2)
Not known	30 (3.3)	13 (4.6)	17 (2.8)
Diabetes			
No	675 (75.3)	210 (75.5)	465 (75.5)
Yes	221 (24.7)	70 (25.0)	151 (24.5)

[a]Within total sample. [b]Within the relapse TB who had unsuccessful treatment

Determinant of unsuccessful treatment outcome among relapse TB patients

The study variables were analysed using simple logistic regression and multiple logistic (binary) regression, as shown in Table III. This study identified two factors that were linked to unsuccessful outcomes. The first factor was the lack of sputum examination at 5 months of treatment and upon treatment completion (AOR 1.70; 95% CI 1.19,2.44). The second factor was the type of health facilities: government hospitals and government primary health clinics (AOR 0.06; 95% CI 0.03,0.15) and (AOR 0.02; 95% CI 0.01,0.04), respectively. The absence of Sputum AFB examination after the intensive phase was found to be a confounder as it was statistically significant in simple logistic regression; however, after adjustment was made in multiple logistic regression, this factor was found to be insignificant. The final model of

Table III: Determinants of Unsuccessful treatment outcome among Relapse TB patients

Variables	COR (95% CI) [a]	p-value [a]	AOR (95% CI) [b]	p-value [b]
Socio-demographic factor				
Age, (in years)	1.00 (0.99, 1.01)	0.397	1.00 (0.99, 1.01)	0.613
Gender				
Female	1	ref.	1	ref.
Male	0.44 (0.77, 1.42)	0.799	1.10 (0.78, 1.55)	0.596
Ethnicity				
Chinese	1	ref.	1	ref.
Malay	1.06 (0.69, 1.62)	0.799	0.66 (0.43, 1.00)	0.052
Indian	0.70 (0.41, 1.19)	0.187	0.68 (0.41, 1.13)	0.133
Others	0.64 (0.32, 1.27)	0.201	0.56 (0.30, 1.04)	0.068
Clinical factor				
DOTS (intensive)				
Yes	1	ref.	1	ref.
No	1.34 (0.92, 1.96)	0.133	1.06 (0.65, 1.74)	0.811
Type of health facilities				
Private	1	ref.	1	ref.
Government Hospital	0.06 (0.03, 0.15)	<0.001 *	0.06 (0.03, 0.15)	<0.001 *
Government Primary Health Clinic	0.01 (0.01, 0.04)	<0.001*	0.02 (0.01, 0.04)	<0.001 *
Sputum AFB at 2 month				
Negative	1	ref.	1	ref.
Positive	1.28 (0.61, 2.71)	0.52	1.62 (0.68, 3.85)	0.272
Not done	1.51 (1.09, 2.11)	0.015 *	0.98 (0.62, 1.56)	0.934
Sputum AFB at ≥ 5 month				
Negative	1	ref.	1	ref.
Positive	1.84 (0.53, 6.42)	<0.001 *	2.10 (0.54, 8.10)	0.282
Not done	1.89 (1.41, 2.54)	<0.001 *	1.70 (1.19, 2.44)	0.004 *

AOR (Adjusted Odds Ratio), Confidence Interval (CI). The Cox & Snell R2 value is 0.150, indicating the proportion of variance explained by the model. The Hosmer and Lemeshow test yield a value of 0.687, suggesting good model fit. Classification: 73.5%, and the Area Under the Curve (AUC) is 70.0% (95% CI: 66.0-74.0; p-value=<0.001). [a]Test employed: Simple logistic regression [b]Test employed: Multiple Logistic Regression Analysis (Enter Method) Constant value: 0.842 and the model assumption is met. There is a no interaction and multicollinearity.

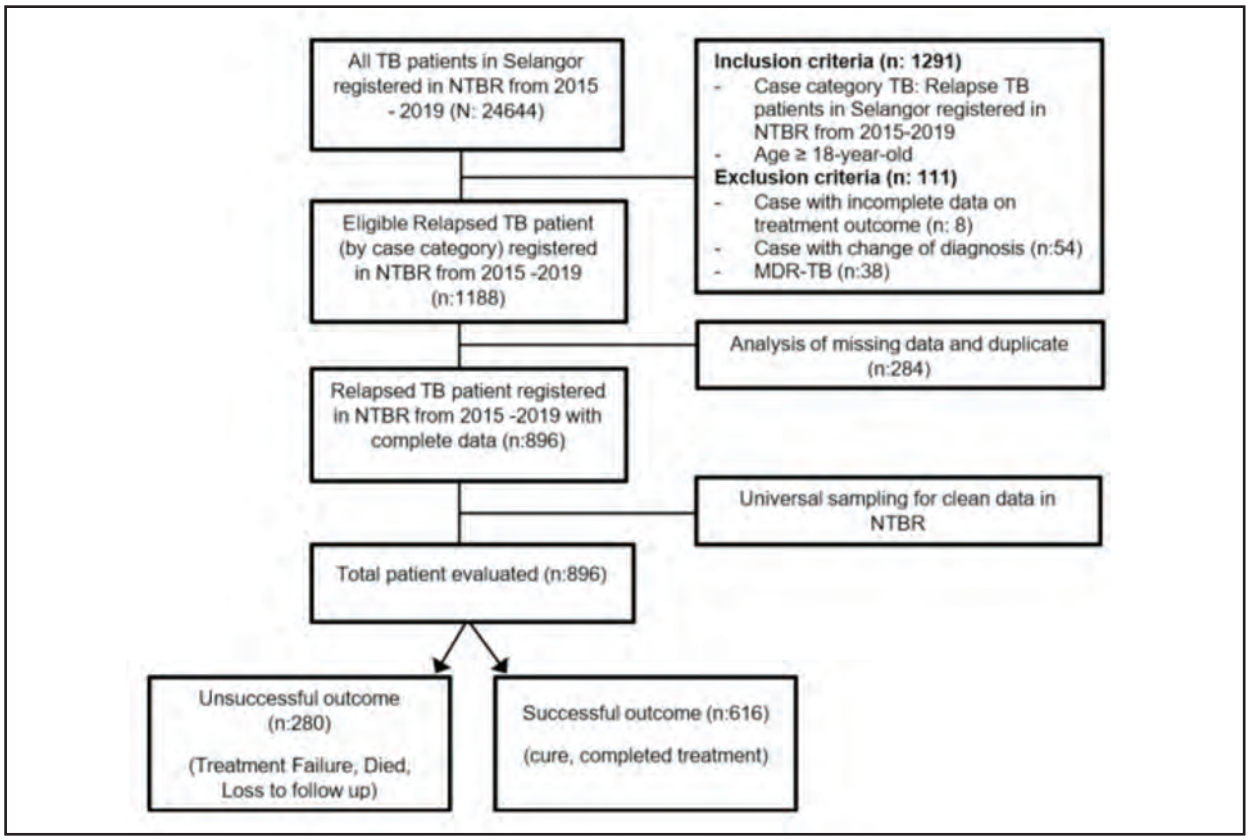

Fig. 1: Flow chart of data retrieval and extraction

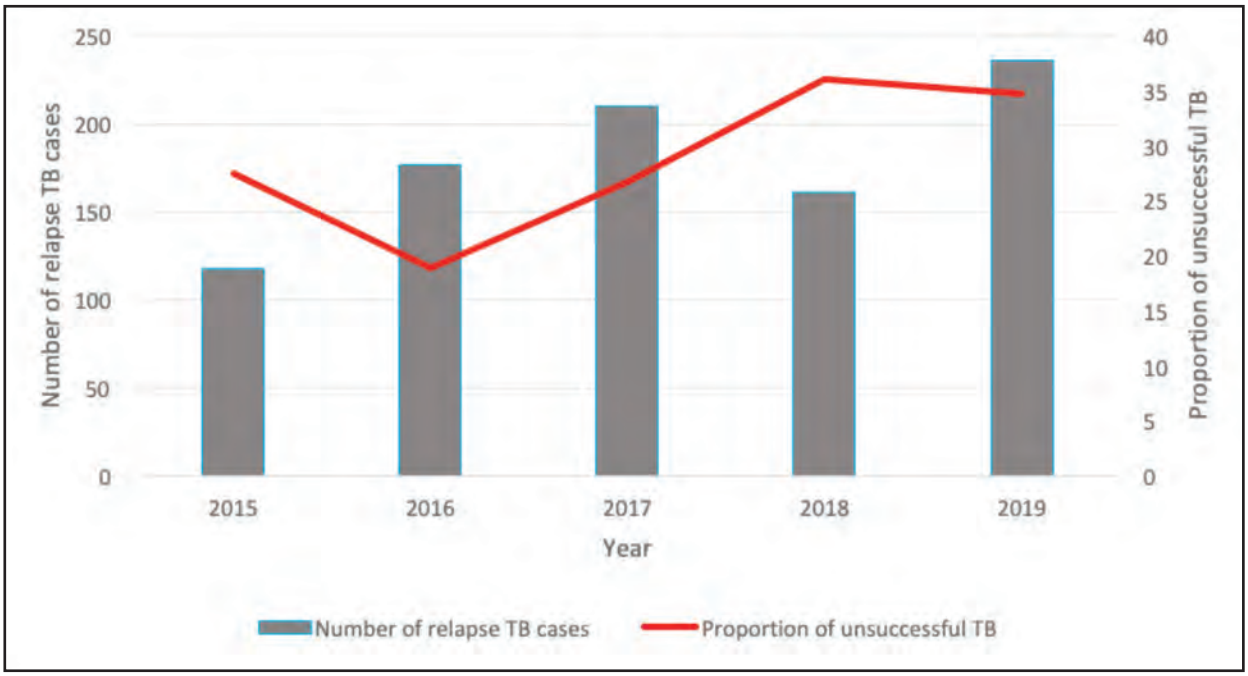

Fig. 2: Trends of unsuccessful treatment outcome among relapse TB cases in Selangor from 2015 -2019

determinants comprised all significant factors and three clinically relevant factors: age, gender, and DOTs during the intensive phase.28-30 The prediction of this model was 70% (95% CI 66.4, 73.7).

DISCUSSION

In this retrospective cohort study, we highlighted the high proportion of unsuccessful treatment outcomes among relapse TB patients in Selangor. The increasing trends seen were alarming, especially from the year 2016 to the year 2019 (18.8%, 26.7%, 36%, and 34%), respectively. One of the critical indicators being monitored to achieve target under the End TB strategy by WHO is a successful TB treatment rate of 90%, thus allowing only 10% of unsuccessful rate.[31] A study done using Malaysia's national-wide data (2014 until 2017), revealed a high rate of unsuccessful treatment outcomes among relapse TB patients compared to new patients (22.9% and 18.5%) respectively.[21] This current study suggests that Selangor had a high rate of unsuccessful treatment outcome that was above the national level.

A study from Tanzania utilizing national wide data however reported much lower rate of unfavourable outcome among relapse TB patients compared to Malaysia which was 10%.[11]

Factors associated with unsuccessful treatment outcomes among relapse TB patients

We found that not doing Sputum AFB examination after 5 months and before the end of treatment, was associated with a higher likelihood of unfavourable outcomes in relapse TB patients AOR 1.70 (95% CI: 1.19,2.44). Furthermore, the current study revealed that 55% of relapse TB patients that had not been checked for sputum at 5 month and beyond reported much higher rate of incomplete monitoring compared to a study done in Uganda that showed 16% of patients did not have sputum AFB follow up at 2 months, 39% at 3 months and 28% at 5 months and later. Lack of proper sputum monitoring has been linked to not being on DOTs, inability to produce sputum, long time spent at the laboratory, and poor health education among patients and health care providers.[32] In Malaysia, for instance, according to the Clinical Practice Guideline (CPG) of Management of Tuberculosis, all patients with pulmonary tuberculosis must undergo routine monitoring during their treatment. This includes monitoring the presence of acid-fast bacilli (AFB) in sputum samples at specific intervals: during the initial assessment stage, after 2 weeks of commencing treatment, after 1 month, after 5 months, and at the end of treatment. This is in line with WHO's recommendation to use sputum smears to evaluate treatment outcomes and monitor the result of the treatment.[25,33]

This study also found that being treated in government facilities that include government hospital and government primary health clinic were protective factor for an unsuccessful treatment outcome in relapse TB patients AOR 0.06 (95% CI 0.03, 0.15) and 0.02 (95% CI 0.01, 0.04) respectively compared to being treated in private facilities.

A mixed method study done in Nigeria[33] found that most patients diagnosed with TB in private sectors were referred to public facilities while 25% being treated in private facilities and reported that 10.5% of patient were treated with unconventional regimens, 21% were cured, 11% died, 16% loss to follow up and 53% were not evaluated. This study revealed that 5% of patients received unconventional treatment regimens, 21% of the patients were cured, 11% died, 16% defaulted, and 53% were not assessed.

The knowledge about TB among the healthcare providers was not up to date, and most of the healthcare providers had not undergone any formal training in tuberculosis.[34,35] Most patients that were suspected or confirmed to have TB were referred to the public sector without any feedback.[33] Also, the private healthcare providers were not very sure of the diagnostic procedures and necessary tests for the definite diagnosis of TB.[36]

The findings are in line with other previous studies conducted in Malaysia's high TB burden neighbouring countries such as Indonesia and Pakistan.[37,38] have also pointed to shortcomings in the diagnosis, management and treatment of TB patients by private practitioners. It was reported that 19-53% of TB cases and about 4-18% of smear-positive Pulmonary TB cases were not treated with standardized diagnosis and treatment.[37] A systematic review was conducted in India, which reported barriers to engagement with private sectors in TB care includes lack of coordination mechanisms and inadequate knowledge of private practitioner on programmatic aspects.[34]

The study finding highlights the lack of routine sputum smear examination upon completion of 5 months of treatment and upon treatment completion. It is a predictor for poor treatment outcomes in relapse TB patients and signifies the importance of the clinical managing team adhering to the recommendations suggested by the CPG, which are routine monitoring of sputum smears being practiced, including the procedure to induce sputum in patients who have difficulty to produce the phlegm.

Apart from that, this study also highlighted the increased risk of unsuccessful treatment outcomes associated with private treatment facilities; this signifies that strengthening the multisectoral and TB public-private partnership and regular training to have updates on recent knowledge is important. TB program managers, public and private practitioners, and NGOs all have a critical role in TB prevention and Control efforts and to end TB epidemics.

The strength of our study is that it is the first study done in Selangor focusing solely on relapse TB patients and its associated factors for unsuccessful treatment outcomes. This evidence would be beneficial for TB Control teams to plan out tailored strategies and approaches specific to this group of patients which have a higher risk of unsuccessful treatment.

A limitation of our study is that this study utilized secondary data that have limited variables, for example, the factors that can affect the adherence to TB medication, including side effects of TB regimes, other comorbidities associated with TB, such as alcohol abuse, and chronic obstructive pulmonary disease.

CONCLUSION

This study has identified one of the determinants of unsuccessful treatment among relapse TB patients is the lack of routine sputum smear examination after completing 5 months of therapy, and being treated in government facilities is a protective factor. The study also highlights the high proportion of unsuccessful treatment outcome among relapse TB patients and the importance of adherence to routine sputum monitoring and strengthening public-private partnerships.

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The ten-year cardiovascular disease risk prediction among primary healthcare workers using the office-based globorisk tool: A cross-sectional study

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) remain to be the leading cause of premature mortality worldwide, and healthcare workers (HCWs) are potentially at risk for developing CVDs. Office-based Globorisk is a ten-year risk prediction tool for CVDs risk scores. This present study aims to determine the prevalence of CVDs risk and risk factors associated with moderate-high CVDs risk among primary HCWs in government health clinics in Selangor.

Materials and Methods: A cross-sectional study was conducted on 543 HCWs from the KOSPEN WOW ("Komuniti Sihat Pembina Negara" or "Healthy Community Builds the Nation-Wellness of Workers") database in three district health offices (DHOs) under the Selangor State Health Department in Malaysia. To estimate the office-based Globorisk model, factors such as age, sex, current smoking status, systolic blood pressure (SBP), and body mass index (BMI) were included. Data analysis employed were Pearson chi-square test, Fisher's exact test, Welch's t-test and binary logistic regression.

Results: Among 543 participants, 453 (83.4%) were female, 439 (80.8%) were Malay with mean (SD) age of 44.4 (4.38). Majority of moderate-high CVDs risk identified among primary HCWs was male with 26 (86.7%), Malay with 25 (83.3%), and non-clinical group with 17 (56.7%). The prevalence of low CVDs risk was 94.5% (95% CI: 92.2–96.2) and 5.5% (95% CI: 3.8–7.8) for the moderate-high risk category. Factors associated with moderate-high CVDs risk were job category with non-clinical group (95% CI: 1.43, 6.85), elevated blood glucose (95% CI: 3.25, 19.41) and anxiety symptom (95% CI: 1.46, 13.86).

Conclusion: The KOSPEN WOW platform is effective for screening and guiding implementation of intervention programmes to prevent CVDs.

KEYWORDS:
Cardiovascular disease risk, primary healthcare workers, office-based Globorisk, KOSPEN WOW

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of heart and blood vessel disorders, including coronary heart disease, cerebrovascular disease, rheumatic heart disease, peripheral arterial disease, and congenital heart disease.[1] CVDs remain to be the leading cause of premature mortality worldwide, resulting in over 20 million deaths and more than 400 million disability-adjusted life-years (DALYs) lost in 2021.[2] In Malaysia, cardiovascular and circulatory diseases, including ischemic heart disease (17.7%) and cerebrovascular disease or stroke (8.0%), were the primary causes of years of life lost (YLL).[3]

Healthcare workers (HCWs) are potentially at risk of developing CVDs[4] due to high prevalence of CVDs risk factors. Studies among HCWs reported that 45.6% of primary HCWs practiced sedentary lifestyle[5], 54.2 % were overweight and obese[6], 46.7% had high blood glucose[4], and 72.7% were smokers.[4] HCWs were also more susceptible to psychological problems such as depression[7] and stress[8] which contributes to an increase of CVDs risk. In addition, a prior study also indicated that the prevalence of CVDs risk among HCWs in a tertiary healthcare facility in Kuala Lumpur was significant, with 30.8% of the HCWs classified as having a moderate and high ten-year CVDs risk.[4]

The Ministry of Health Malaysia (MOH) established the KOSPEN WOW ("Komuniti Sihat Pembina Negara" or "Healthy Community Builds the Nation Wellness of Workers"), a comprehensive workplace health intervention programme aimed at reducing the burden of Non-Communicable Diseases (NCDs) such as CVDs and related risk factors among employees.[9] There is a total of eight components in the KOSPEN WOW programme including health screening as one of the scopes, which is a good initiative to be able to detect CVDs risk in the early stages.[9] HCWs in government health clinics, whether clinical or non-clinical, will undergo general health screenings at least once a year through this scope in the KOSPEN WOW programme.[9] The Occupational Safety and Health (OSH) Unit is responsible for ensuring the HCWs undergo health screenings, including anthropometric measurements, blood pressure, waist circumference, capillary glucose level, alcohol

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and smoking status, as well as psychological screening in terms of stress, depression and anxiety.[9] The other seven components of KOSPEN WOW intervention activities, such as healthy eating, non-smoking practice, active living, weight management, healthy mind, healthy workplace, as well as prevention and reducing harmful use of alcohol are applied based on the risk detected from the health screenings.[9]

Globorisk tool, including office-based and laboratory-based calculators, is effective for calculating CVDs risk.[11] The office-based Globorisk tool is useful when there is limited resources for blood testing.[12] Comparative studies between Globorisk and other CVDs risk tools showed that the Globorisk had good agreement with WHO risk scores[13] and moderate agreement with Framingham Risk Score.[14] Globorisk had low sensitivity (27.5%[15] and 21.9%[16]) and high specificity (89.0[15] and 94.2%[16]) indicating that it is still a useful tool in CVDs risk screening.

According to WHO, an estimated 80% of CVDs is preventable and ideally CVDs risk among HCWs were expected to be low due to their adequate knowledge of CVDs risk prevention.[17] However, despite their adequate knowledge and awareness of health, HCWs had a high prevalence of moderate and high ten-year CVDs risk[4], including risk factors such as practicing a sedentary lifestyle[5], being overweight or obese[6], having high blood glucose[4], and smoking.[4] High prevalence of CVDs and its risk factors may cause low quality of life[18], disrupt the quality of services, and leads to life-threatening complications.[3] Majority of the CVDs risk studies in Malaysia were conducted at tertiary settings,[4] and there were limited studies focusing on the primary HCWs. This study would also investigate psychological distress among HCWs and its association with CVDs risk, which has not been previously studied. The objectives of this study were to determine the prevalence of CVDs risk and risk factors associated with moderate-high CVDs risk among primary HCWs in government health clinics in Selangor, Malaysia.

MATERIALS AND METHODS

Study Design

This etiological research used a cross-sectional study design to determine the prevalence of CVDs risk and risk factors associated with moderate-high CVDs risk among primary HCWs in Selangor, Malaysia. This study was conducted by obtaining secondary data from the KOSPEN WOW database under the Selangor State Health Department, Malaysia.

Location and Study Population

This study was conducted by randomly selecting three DHOs out of nine DHOs in Selangor State, Malaysia. The secondary data was extracted from the selected DHOs, Petaling, Hulu Langat and Kuala Selangor. The study population was primary HCWs working in government health clinics who fulfilled the inclusion and exclusion criteria. The inclusion criteria were: i) HCWs aged ≥ 40 years old (requirement from office-based Globorisk calculator); ii) must have undergone KOSPEN WOW general health and mental health screening from 1 January 2023 to 31 May 2024. Meanwhile, the exclusion criteria were: i) HCWs with incomplete data needed for office-based Globorisk calculator; ii) known history of CVDs and; iii) workers who were not employed under the Ministry of Health, Malaysia such as cleaner or security guard.

Sample size

Sample size was estimated by using Open Source Epidemiologic Statistics for Public Health (OpenEpi) software for a single population proportion. The estimated primary HCWs population in Selangor is 7000. Based on a previous study by Che Muhammad et al, 2022, the prevalence of high CVDs risk among the population using Globorisk was 48.9%, and by taking the confidence interval of 95%, power of 80%, and 5% absolute precision, the estimated sample size required was 365. An additional 20% was included to the final sample size estimation to compensate any incomplete data, hence the minimum sample size required in this study was 438 subjects.

Universal sampling method was applied by including all sample from Petaling, Hulu Langat and Kuala Selangor DHOs who fulfilled the inclusion and exclusion criteria.

Data Collection

The collection of secondary data from KOSPEN WOW database was conducted at the Occupational Safety and Health (OSH) unit of the Selangor State Health Department, as well as from the Petaling, Hulu Langat, and Kuala Selangor DHOs.

Study Variables

The study's outcome, CVDs risk by definition, was a ten-year risk prediction for CVDs among primary HCWs working at government health clinics in Selangor. The CVDs risk scores were calculated using the office-based Globorisk tool and then categorized into low and moderate-high risk.[18] A score less than 10% indicated low risk, and more than 10% indicated moderate-high risk prediction to develop CVDs in a ten-year period.[19] The data required for office-based Globorisk calculator included height (cm), weight (kg), gender, age ≥40 years old , smoking status (yes or no), and systolic blood pressure for the CVDs risk calculation.

The independent variables were divided into three groups: sociodemographic factors, such as ethnicity, job category, and family history of CVDs; lifestyle-related behaviours, such as alcohol consumption; and health-related factors, including a known case of diabetes mellitus (DM), hypertension (HPT), high cholesterol, waist circumference (WC), capillary blood glucose level, and psychological assessment. The psychological assessments were conducted by utilizing validated Whooley questionnaires for depression and the General Anxiety Disorder-2 (GAD-2) questionnaire for anxiety screening.

Data Management

Secondary data without identifiers from the KOSPEN WOW database were obtained from the data owner at the OSH Unit in Petaling, Hulu Langat and Kuala Selangor DHOs. The data was compiled into a Microsoft Excel Open XML Spreadsheet (xlsx) format. The process of data cleaning and checking missing data was conducted. Listwise deletion was used for missing data required for Globorisk calculator. The

Table I: Characteristics of primary HCWs in Selangor according to CVDs risk outcomes

Variables	CVDs risk			p-value
	Low (n=513) n (%)	Moderate-high (n=30) n (%)	Total (n=543) n (%)	
Sociodemographic factors				
Age (years)[a]	44.2 (4.14)	49.1 (5.62)	44.4 (4.38)	<0.001[d]
40-44	337 (65.7)	5 (16.7)	342 (63.0)	
45-49	118 (23.0)	10 (33.3)	128 (23.6)	
50-54	40 (7.8)	6 (20.0)	46 (8.5)	
55-59	18 (3.5)	9 (30.0)	27 (5.0)	
Gender				
Female	449 (87.5)	4 (13.3)	453 (83.4)	<0.001[c]
Male	64 (12.5)	26 (86.7)	90 (16.6)	
Ethnicity				
Malay	414 (80.7)	25 (83.3)	439 (80.8)	0.722[b]
Non-Malay	99 (19.3)	5 (16.7%)	104 (19.2)	
Job category				
Clinical	374 (72.9)	13 (43.3)	387 (71.3)	<0.001[b]
Non-clinical	139 (27.1)	17 (56.7)	156 (28.7)	
Family history of CVDs				
No	469 (91.4)	28 (93.3)	497 (91.5)	
Yes	44 (8.6)	2 (6.7)	46 (8.5)	1.000[c]
Lifestyle-related behavior				
Smoking				
No	504 (98.2)	18 (60.0)	522 (96.1)	<0.001[c]
Yes	9 (1.8)	12 (40.0)	21 (3.9)	
Alcohol consumption				
No	459 (89.5)	26 (86.7)	485 (89.3)	0.549[c]
Yes	54 (10.5)	4 (13.3)	58 (10.7)	
Health-related factors				
Height (m)[a]	1.58 (0.07)	1.67 (0.10)	1.59 (0.08)	<0.001[d]
Weight (kg)[a]	69.7 (14.27)	84.8 (18.86)	70.6 (14.94)	<0.001[d]
BMI (kg/m^2)[a]	27.9 (5.35)	30.2 (4.60)	28.0 (5.33)	0.01[d]
Normal	157 (30.8)	3 (10.0)	160 (29.7)	0.033[b]
Overweight	199 (39.1)	13 (43.3)	212 (39.3)	
Obesity	153 (30.1)	14 (46.7)	167 (31.0)	
Waist circumference (cm)				
Malea	88.2 (12.69)	100.7 (17.77)	91.8 (15.32)	<0.003[d]
Femalea	87.8 (12.23)	93.1 (9.65)	87.8 (12.21)	0.351[d]
Elevated waist circumference				
Yes	360 (70.2)	21 (70.0)	381 (70.2)	0.984[b]
No	153 (29.8)	9 (30.0)	162 (29.8)	
Blood glucose (mg/d)[a]	5.4 (1.01)	7.5 (3.93)	5.5 (1.43)	<0.005[d]
Elevated blood glucose				
No	363 (70.8)	7 (23.3)	370 (68.1)	<0.001[b]
Yes	150 (29.2)	23 (76.7)	173 (31.9)	
Blood pressure (mmHg)				
SBP[a]	119.9 (10.56)	136.9 (15.42)	120.8 (11.54)	<0.001[d]
DBP[a]	75.4 (11.26)	78.1 (22.93)	76.1 (10.29)	0.616[d]
Elevated BP				
Yes	307 (59.8)	28 (93.3)	335 (61.7)	<0.001[b]
No	206 (40.2)	2 (6.7)	208 (38.3)	
Known case of DM				
No	473 (92.2)	22 (73.3)	495 (91.2)	0.003[c]
Yes	40 (7.8)	8 (26.7)	48 (8.8)	
Known case of HPT				
No	440 (85.8)	21 (70.0)	461 (84.9)	0.032[c]
Yes	73 (14.2)	9 (30.0)	82 (15.1)	
Known case of high cholesterol				
No	478 (93.2)	24 (80.0)	502 (92.4)	0.019[c]
Yes	35 (6.8)	6 (20.0)	41 (7.6)	
Depression				
No	458 (89.3)	25 (83.3)	483 (89.0)	0.361[c]
Yes	55 (10.7)	5 (16.7)	60 (11.0)	
Anxiety				
No	483 (94.2)	25 (83.3)	508 (93.6)	0.036[c]
Yes	30 (5.8)	5 (14.3)	35 (6.4)	

Abbreviation: SD = standard deviation, CVDs = cardiovascular disease, DM = diabetes mellitus, HPT = hypertension
[a]Mean (SD), [b]Chi-square Test, [c]Fisher's Exact Test, [d]Welch's t-test

Table II: Factors associated with moderate-high CVDs risk among primary HCWs in Selangor (n=543)

Variables	Simple logistic regression			
	B (SE)	Wald (df)	Crude OR (95% CI)	p-value
Sociodemographic factors				
Ethinicity				
Malay	0.18 (0.50)	0.13 (1)	1.2 (0.45, 3.20)	0.722
Non-Malay			1	
Job category				
Non-clinical	1.26 (0.38)	10.87 (1)	3.52 (1.67, 7.43)	<0.001
Clinical			1	
Family history of CVDs				
No	0.27 (0.749)	0.13 (1)	1.31 (0.30, 5.70)	0.716
Yes			1	
Lifestyle-related behavior				
Alcohol consumption				
Yes	0.27 (0.56)	0.23 (1)	1.31 (0.44, 3.89)	0.629
No			1	
Health-related factors				
Elevated WC				
Yes	0.48 (0.47)	1.07 (1)	1.62 (0.65, 4.05)	0.3
No			1	
Elevated blood glucose				
Yes	2.07 (0.44)	21.96 (1)	7.95 (3.34, 18.93)	<0.001
No			1	
Known case of DM				
Yes	1.459 (0.44)	10.77 (1)	4.3 (1.8, 10.28)	0.001
No			1	
Known case of HPT				
Yes	0.95 (0.42)	5.16 (1)	2.59 (1.14, 5.86)	0.023
No			1	
Known case of high cholesterol				
Yes	1.23 (0.49)	6.31 (1)	3.41 (1.31, 8.9)	0.012
No			1	
Depression				
Yes	0.51 (0.51)	1.00 (1)	1.67 (0.61, 4.53)	0.317
No			1	
Anxiety				
Yes	1.17 (0.53)	5.00 (1)	3.22 (1.15, 9.01)	0.026
No			1	

Abbreviation: B = Beta, SE = standard error, df = degree of freedom, OR = odd ratio, CI = confidence interval, CVDs = cardiovascular disease, WC = waist circumference, DM = diabetes mellitus, HPT = hypertension

Statistical test = Simple logistic regression, statistical significant = p-value <0.05

Table III: Factors associated with moderate-high CVDs risk among primary HCW in Selangor (n=543)

Variables	B(SE)	Wald (df)	Adj. OR (95% CI)	p-value
Sociodemographic factors				
Job category				
Non-clinical	1.14 (0.399)	8.174 (1)	3.13 (1.43, 6.85)	0.004
Clinical			1	
Elevated blood glucose				
Yes	2.07 (0.46)	20.67 (1)	7.94 (3.25, 19.41)	<0.001
No			1	
Anxiety				
Yes	1.50 (0.57)	6.88 (1)	4.50 (1.46, 13.86)	0.009
No				

Abbreviation: B = Beta, SE = standard error, df = degree of freedom, Adj.= Adjusted, OR = odd ratio CI = confidence interval,
Hosmer and Lemeshow test: 0.626, No interaction or multicollinearity
Statistical test = Multiple logistic regression, Statistical significant = p-value <0.05
*Refer Table II for significant variables selected into the multiple logistic regression model.

final sample (n=543) were transferred and analysed using Statistical Package for the Social Sciences (SPSS) software version 29.0 IBM SPSS Inc..

To safeguard the privacy and confidentiality of the subjects, the researcher received data from the data owner without any identifier such as name, NRIC number, telephone number or home address. Identification running number for example "1, 2, 3…" were used to identify the subjects. The data received were safely kept in a password-protected computer, and only the research team members were able to access the data.

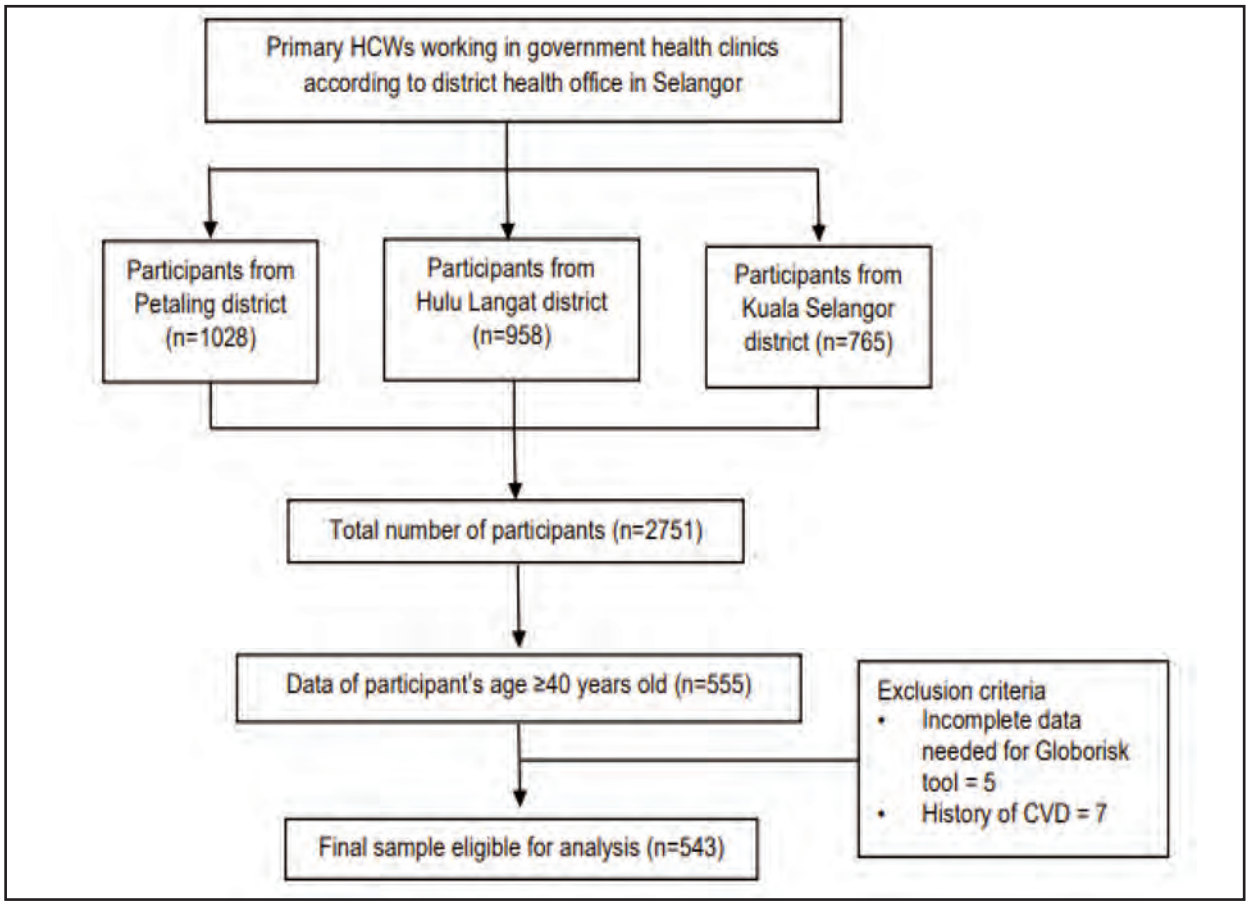

Fig. 1: Flow diagram of participants selection

Statistical Analysis

Descriptive and inferential statistics analysis were conducted using IBM Statistical Package for the Social Sciences (SPSS) Inc. version 29.0. Descriptive statistics analysis was used to describe the prevalence and characteristics of CVDs risk among the study participants. The characteristics of primary HCWs according to CVDs risk were presented as proportions in frequency and percentages (%) for categorical variables. On the other hand, continous variables were presented as mean with standard deviation (SD).

Inferential statistics analysis was conducted to determine risk factors associated with moderate-high CVDs risk among primary HCWs. Univariate analyses were conducted by using Pearson chi-square or Fisher's exact test for categorical variables and Welch's t-test for continuous variables. Multivariable analysis, binary logistic regression was used to identify factors associated with moderate-high CVDs risk. Variables were included in the multiple logistic regression model based on a statistically significant p-value <0.05 in the simple logistic regression. Variable selection was conducted using the backward elimination method. The preliminary model was tested for linearity in the logit, interaction, and multicollinearity. The model's fitness was determined using the Hosmer-Lemeshow goodness-of-fit test and the receiver operating characteristic (ROC) curve. The strength of association between each risk factors and outcome measure was reported as crude or adjusted odds ratios (OR), 95% confidence intervals (CI), and their corresponding p-values. The significance level for the statistical test was set at p-value <0.05.

Ethics Approval

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. The ethical approval from UiTM Research Ethics Committee (REC) - (FERC-EX-24-08) and Medical Research and Ethic Committee (MREC) - NMRR ID-24-00930-EVZ (IIR) were obtained for this study.

RESULTS

Figure 1 shows the flowchart diagram of participant selection from three DHOs in Selangor, Malaysia. A total of 543 participants were analysed with 513 categorised as low-risk and 30 in the moderate-high risk category for the ten-year CVDs risk prediction. The prevalence of CVDs risk among the participants was 94.5% (95% CI: 92.2–96.2) for the low-risk category and 5.5% (95% CI: 3.8–7.8) for the moderate-high-risk category. The characteristics of the primary HCWs in Selangor are shown in Table I with most participants being female 453 (83.4%), Malay ethnicity 439 (80.8%), mean (SD) for age of 44.4 (4.38). Majority of primary HCWs with

moderate-high CVDs risk were male, with 26 (86.7%), malay ethnicity, 25 (83.3%), non-clinical group, 17 (56.7%), and obesity, with a mean BMI of 30.2 kg/m^2.

Table II shows factors associated with moderate-high CVDs risk among primary HCWs in Selangor. The simple logistic regression analysis produced a significant p-value <0.05 for six independent variables, prompting a subsequent multiple logistic regression analysis. The factors that were significant included sociodemographic factors; non-clinical job category with crude OR 3.52 (95% CI: 1.67, 7.43) and health-related factors; elevated blood glucose with crude OR 7.95 (95% CI: 3.34, 18.93), history of DM with crude OR 4.3 (95%CI: 1.8, 10.28), HPT with crude OR 2.59 (95% CI: 1.14, 5.86), and hypercholesterolemia with crude OR 3.41 (95% CI: 1.31, 8.9), as well as symptoms of anxiety with crude OR 3.22 (95% CI: 1.15, 9.01).

Table III displays the results of the multivariable analysis which showed three significant factors after adjustment of confounders, including non-clinical job category with aOR 3.13 (95% CI: 1.43,6.85), elevated blood glucose with aOR 7.94 (95% CI: 3.25, 19.41) and anxiety symptoms with aOR 4.50 (95% CI: 1.46, 13.86). We found that other factors that were not significant, including known case of DM, HPT and high cholesterol were confounders in this study.

DISCUSSION

The prevalence of moderate-high risk of developing CVDs among the primary HCWs was found to be lower compared to previous studies conducted in a tertiary center in Kuala Lumpur[4] and among the general Malaysian population.[19] This contrast could be due to an imbalanced proportion of HCWs, with the majority of the workers in government health clinics in Selangor being young age and female that contributed to lower CVDs risk.[21]

From the current findings, 61.7% of primary HCWs had modifiable CVDs risk factor, including elevated BP (≥140/90 mmHg). This findings were higher than the KOSPEN WOW 2022 report, where only 19% of the general workers in Malaysia had elevated BP.[9] Despite their good knowledge and perception of health, HCWs were at risk of developing hypertension as they tend to consume fast foods and lack of physical activity duration.[23] Future health promotion programmes must be implemented, with a focus on changing lifestyle behaviours such as adopting healthy eating habits and engaging in active physical activity.

This study also found that primary HCWs in Selangor were mostly overweight and obese, including abdominal obesity with a waist circumference of ≥80 cm in females and ≥90 cm in males. These findings are consistent with other study findings in Africa[24], Palestine[25] and Malaysia[6,26] with more than half of the HCWs being overweight and obese. The high prevalence of overweight and obesity among primary HCWs is a growing concern to MOH as Malaysia was even ranked as the most obese country in Southeast Asia.[27] On top of that, HCWs were also found to have abdominal obesity, which is related to developing other CVDs risk factors, including HPT, DM, hypercholesterolemia, and obstructive sleep apnea (OSA).[28,29] The effects of OSA for example may cause a reduction in workplace performance ability, loss of focus and memory, fatigue, and emotional disturbance.[30] Furthermore, individuals with a normal BMI but a high waist circumference have poor life expectancy than overweight or obese individuals who do not have abdominal obesity.[31] Therefore, a vigorous weight reduction programme among HCWs should not only target a normal BMI but also to achieve a normal waist circumference.

Our analysis showed that job category had a significant association with higher CVDs risk, with non-clinical HCWs having a higher odd to develop moderate-high risk of CVDs compared to the clinical group. A similar finding was found in Singapore, which showed that the modifiable risk factors for CVDs among non-healthcare professional were higher.[32] This is due to the fact that HCWs in hospitals were required to move around frequently, compared to those in health clinics who were less physically active.[5] Other than that, knowledge of CVDs is higher among the clinical group compared to the non-clinical group, which is related to their better attitude and perception about the disease.[33] Hence, it is crucial to prioritise health awareness and educational activities to enhance non-clinical HCWs' understanding of the issues before inviting them to join the programme aimed at mitigating the risk of CVDs.

This study also showed that primary HCWs with elevated capillary blood glucose levels during KOSPEN WOW screening had a significant association with an increased risk of CVDs. High glucose levels were associated with the progression of atherosclerosis or heart failure, which will lead to increased CVDs risk.[34] A hospital-based study conducted in Taiwan showed that there was a significant increase in blood glucose plasma among HCWs following the COVID-19 pandemic.[35] Due to workplace burden, HCWs were prone to chronic exhaustion, which affected their health behaviour, reduced their time for exercise, and led to unhealthy eating habits that resulted in elevated blood glucose levels.[35] Therefore, a preventative programme must target this group of HCWs to prevent them from developing DM as well as reduce the risk of CVDs.

Psychosocial factor was another factor that we found to have significant association with moderate-high risk of developing CVDs. Primary HCWs with anxiety had a 4.5 times odd to develop moderate-high CVDs risk compared to those without the condition. This was in congruent with other similar studies in German[36] and United States[37] communities, where generalized anxiety disorder (GAD) was significantly associated with CVDs. Anxious individuals tend to develop sympathetic nervous system hyperactivity, which can overstimulate heart rate and blood pressure, leading to the rapid progression of atherosclerosis.[38] In contrast, another study suggested anxiety as a cardio-protective factor in the CVDs context, where it reduced the risk of myocardial infarction.[39] This was related to a situation where anxiety arose due to a CVDs diagnosis whereby people tend to focus more on their health and took protective measures to avoid the CVDs events.[39] Although depression was found not to be significant, proper assessment and treatment of depression and anxiety symptoms among primary HCWs is necessary to

prevent further health deterioration that may result in increased risk of CVDs.

This study indicated that the office-based Globorisk calculator is a valuable tool for predicting ten-year CVDs risk in primary HCWs over 40 years of age. We proposed that the estimation of CVDs risk should be mandatory via the use of this instrument. Moreover, the intervention planning strategies aimed at combating CVDs should prioritise the non-clinical HCWs due to their associated risk of developing a higher CVDs risk. We encourage the DHOs to implement the intervention strategies outlined in the KOSPEN WOW component, such as the promotion of active living, healthy eating, and weight management. It is also crucial to ensure that a significant number of primary HCWs participate in these intervention activities and to make it compulsory for those who are at risk. Furthermore, the intervention strategy must involve the participation of all HCWs to achieve an ideal waist circumference, which can serve as an effective foundation for a weight loss program. For instance, DHOs or MOH may mandate that all HCWs must achieve and maintain an ideal waist circumference as a component of workplace requirements. We also recommend that psychological distress, such as anxiety and depression among HCWs need to be properly assessed, and if the root cause is work-related, a proactive intervention must be implemented. Proactive interventions may include collaborative care, whereby an interprofessional team collaboratively manages cases and monitors HCWs, task or workplace shifting as necessary, and referral to a specialised care for more intensive treatment.[40] We strongly urge that these initiatives and activities require coordination and understanding among all stakeholders to ensure their effectiveness in reducing CVDs risk development among HCWs. This study may provide baseline data for further cohort studies related to CVDs risk involving HCWs.

Strength and limitations

This is the first study in Malaysia that employed office-based Globorisk tool as a CVDs risk prediction among HCWs. This study utilised reliable data obtained from medical officers responsible for yearly health screening among HCWs. The anthropometric and biological measurements were performed using calibrated instruments by well-trained health personnels who presumed to have good clinical skills. The use of a cross-sectional study design limited this study by the inability to establish a temporal relationship and a causality effect between the exposure and outcome. It was also necessary to exercise caution when generalizing the results of this study, as it was conducted in a single state, restricted to the primary HCWs population, imbalance percentage of gender and race where majority was conquered by female and Malay participants. Furthermore, the use of secondary data resulted in a lack of important factors, such as residential type, marital status, household income, stress symptoms, physical activity, and dietary habits, that may have been valuable for this study. Moreover, the lack of data on the percentage of HCWs participating in the health screening could potentially lead to selection bias in this study. The quality of data collected were solely based on the skills of health personnels in charged. Variables such as smoking status, alcohol consumption, history of illness and psychological screening relied on HCWs' responses, where information bias may occur.

CONCLUSION

The three main factors that have an association with a moderate-high risk of CVDs among primary HCWs are the non-clinical group, elevated capillary blood glucose levels, and anxiety. Therefore, it is crucial to employ intervention strategies considering these findings to reduce the risk of developing CVDs among HCWs. The KOSPEN WOW platform is effective for screening and guiding the implementation intervention programmes to prevent CVDs.

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CONFLICT OF INTEREST

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Association of cognitive function impairment in patients with psoriasis: A single-centre study in Malaysia

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin condition often associated with comorbidities that may impact cognitive function. This study aims to determine if psoriasis is associated with the risk of cognitive impairment and to assess the relationship between cognitive impairment and various disease-related factors, including psoriasis severity, disease duration, and the presence of psoriatic arthropathy, using the Virtual Cognitive Assessment Tool (VCAT).

Materials and Methods: A total of 160 individuals were selected, comprising 80 psoriasis patients and 80 controls, matched for age, gender, ethnicity, marital status, education levels, and prevalence of comorbidities. Cognitive function was assessed using the VCAT. The relationship between cognitive impairment and various disease-related factors, including psoriasis severity measured using Psoriasis Area Severity Index (PASI scores), disease duration, and the presence of psoriatic arthropathy, was examined.

Results: The mean VCAT scores for the psoriasis and control groups were 25.38 (SD = 3.18) and 25.94 (SD = 2.67), respectively, with no significant difference between the two groups (p = 0.227). While most cognitive domains showed no significant differences, the VCAT attention sub-score was significantly lower in psoriasis patients (p < 0.05). There was no significant association between psoriasis and cognitive impairment. No significant association was found between cognitive function and PASI scores nor psoriatic arthropathy. A negative association was found between disease duration and VCAT scores, suggesting longer disease duration correlates with lower cognitive function (p = 0.05).

Conclusions: This study did not find broad cognitive impairment in psoriasis patients compared to controls, the specific deficit in attention and its association with the duration of psoriasis warrants further investigation. Understanding and addressing the cognitive aspects of psoriasis could significantly improve the overall quality of life for these patients.

KEYWORDS:
Psoriasis, arthropathy, cognitive impairment, Virtual Cognitive Assessment Tool (VCAT)

INTRODUCTION

Psoriasis, a chronic inflammatory skin disorder affecting 0.91%–8.5% of adults, exhibits diverse clinical manifestations. Its onset typically peaks between 20 and 30 years and again between 50 and 60 years, although it can occur at any age.[1] The most prevalent subtype, chronic plaque psoriasis, presents as erythematous plaques with silvery-white scales, often involving the scalp and extensor surfaces. Approximately 20% of patients experience psoriatic arthropathy.[2] Psoriasis is primarily diagnosed clinically, with skin biopsy for confirmation. Its development is influenced by complex genetic and environmental factors, associations with HLA-Cw6, HLA-DR7, HLA-B13, HLA-B17, HLA-B37, and HLA-Bw16.[3]

Psoriasis is a well-known chronic systemic inflammatory disease that is associated with metabolic syndrome and various comorbidities, with particularly pro-inflammatory cytokines and adipocytokines contributing to these conditions.[4] Recent years of research suggest a potential link between psoriasis and cognitive impairment, largely attributed to the cardiometabolic comorbidities that frequently accompany psoriasis, such as hypertension, diabetes, and obesity.[5] It is plausible that the chronic systemic inflammation characteristic of psoriasis, in combination with these cardiometabolic factors, increased the risk of cognitive impairment in affected individuals. Although recent data suggest a higher risk of cognitive impairment and dementia in psoriasis patients, conflicting results exist,[6-9] and there remains a lack of data on cognitive impairment in psoriasis, particularly among Asian populations.

Malaysia's has a highly diverse population, consisting 69.3% Malays, 22.8% Chinese, 6.9% Indians, and 1.0% from other ethnicities.[10] In addition to the Malay language, other commonly spoken languages include English, Mandarin, and Tamil.[11] This linguistic and cultural diversity creates challenges for neuropsychological testing, as the need for translation can alter the accuracy of these assessments. Cognitive tests such as the Mini Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) are standard tools for measuring cognitive function. However, these tests were developed for English-speaking populations, and translating them for use in other languages can compromise their reliability.[12]

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Virtual Cognitive Assessment Tool (VCAT) addresses this issue by offering a visual-based assessment that does not require translation. It evaluates five key cognitive domains—memory, visuospatial function, executive function, language, and attention. VCAT has demonstrated sensitivity and specificity comparable to other tests like MoCA in diagnosing early cognitive impairment. Research shows that VCAT effectively detects cognitive impairment across multilingual and multicultural populations, making it particularly suited to diverse societies.[13] Therefore, this study aimed to investigate the relationship between cognitive impairment and psoriasis using VCAT. In addition, the study also explored the impact of psoriasis severity, presence of psoriatic arthropathy, and duration of psoriasis on cognitive function to shed light on this relatively unexplored aspect.

MATERIALS AND METHODS

Study population

The study was conducted at the dermatology clinic of Sultanah Bahiyah Hospital, Alor Setar, Kedah, from June 2023 to December 2023. A total of 160 participants were enrolled, comprising individuals with psoriasis and an age-sex-matched control group without psoriasis. Inclusion criteria for both groups were individuals aged 18 and above. Psoriasis patients were diagnosed at Sultanah Bahiyah Hospital, while the control group included non-psoriasis patients, their family members, and hospital staff. Exclusion criteria encompassed medical conditions such as stroke, Down syndrome, visual or hearing impairments, severe physical limitations affecting pen-holding ability, and depression (assessed using Patient Health Questionnaire-9 with a score >4).

Sample size calculation

To compare two means, a sample size of 71 (n1) for the baseline/control group and a sample size of 71 (n2) for the other group was required in order to detect the mean difference of 1.75 with a power of 0.80 (80%) and an alpha of 0.05. The mean difference of 1.75 was considered the smallest important difference to be detected. The SD of (the variable of interest) was estimated as 3.70 [7]. This calculation was done using ScalexMean version 1.0.2.[14]

Data collection and study tool

Data were collected using a questionnaire consisting of 3 domains. The first domain is the demographic data of the subjects such as age, gender, marital status, education level, and comorbid conditions; the second domain is the VCAT questions; and the third domain is the Psoriasis Area Severity Index (PASI) [15] and presence of psoriatic arthropathy.

Cognitive function assessment

VCAT was conducted by the principal investigator using the Rater Stimulus Booklet for Memory and the VCAT Scoring Guide. The assessment included 14 questions across five domains: 6 for memory, 2 for language, 3 for executive function, 2 for visuospatial abilities, and 1 for attention. Diagnoses of mild cognitive impairment, dementia, or normal were based on total scores: Dementia (0–19), Mild Cognitive Impairment (20-23), and Normal (24-30).[13]

Dermatological assessment

Patients with psoriasis were clinically diagnosed and measured by using parameters such as PASI,[15] and the involvement of psoriasis arthropathy.[16] PASI categorised severity into mild (PASI <10), moderate (PASI >10 to 20), or severe psoriasis (PASI >20),[17] however Dermatology Life Quality Index (DLQI) was not assessed in this study and PASI is the tool for examine the severity. For the present study, all types of psoriasis were included, and disease duration was determined through patient history.

Statistical analysis

Data collected in this study were analysed using SPSS version 28.0 software. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Parametric data were presented as mean and standard deviation (SD), while non-parametric data were expressed as median + interquartile range (IQR). Descriptive statistics, including mean and SD for numerical variables and percentage distribution for categorical variables, were calculated.

A comprehensive statistical analysis will involve univariate and multivariate regression models. The Logistics regression analysis was used to identify associations between VCAT score and factors such as PASI, psoriatic arthropathy, and total duration of psoriasis. The VCAT score was the dependent variable, and associations with predictor variables were assessed. A p-value <0.05 was considered statistically significant.

Ethical consideration

This study was registered with the National Medical Research Registry Malaysia and was approved by the Medical Research and Ethics Committee, Malaysia (NMRR ID-23-00581-JGY (IIR)).

RESULTS

A total of 160 individuals were recruited for this study, comprising an 80-member psoriasis group and an equally sized control group. Table I summarizes the demographics of both groups. The demographic characteristics were well-matched, with both groups having an average age of 47.2 years and identical gender distribution (46.2% female and 53.8% male). The ethnic composition was predominantly Malay in both groups, with smaller proportions of Chinese, Indian, and other ethnicities. Marital status was also similar, with approximately 78% of participants being married. Educational attainment was comparable between the groups, with slightly more psoriasis patients having completed secondary school (61.3% compared to 50.0% in the control group). Both groups had similar proportions of participants with university education (26.3% in the control group vs. 23.8% in the psoriasis group), while the percentages of those with primary school education or other educational levels were low.

The prevalence of common comorbidities, including hypertension, diabetes mellitus, and dyslipidaemia, was comparable between the psoriasis and control groups. Hypertension was present in 32.5% of the control group and 35.0% of the psoriasis group, while diabetes mellitus was

Table I: Social-demographic data of the participants

Variable	Control (n=80)	Psoriasis (n=80)	p-value
Age, years	47.2 ± 15.5	47.2 ± 15.4	0.996
Gender			1.000
Female	37 (46.2)	37 (46.2)	
Male	43 (53.8)	43 (53.8)	
Ethnic			1.000
Malay	58 (72.5)	58 (72.4)	
Chinese	20 (25.0)	16 (20.0)	
Indian	2 (2.5)	3 (3.8)	
Other	0 (0)	3 (3.8)	
Marital status			0.850
Single	17 (47.2)	19 (52.8)	
Married	63 (50.8)	61 (49.2)	
Education level			0.429
Primary school	8 (10.0)	6 (7.5)	
Secondary school	40 (50.0)	49 (61.2)	
University	21 (26.3)	19 (23.8)	
Other	11 (13.7)	6 (7.5)	
Comorbidities			
Hypertension	26 (32.5)	28 (35.0)	0.867
Diabetes Mellitus	14 (17.5)	17 (21.3)	0.690
Dyslipidaemia	36 (45.0)	30 (37.5)	0.422

Table II: Disease characteristics among psoriasis patients (n = 80)

Variables	n (%)	Mean (SD)	Median (IQR)
Disease onset age, year		32.5 (15.6)	32.0 (23.0)
Disease duration, year *		11.6 (10.7)	9.0 (17.0)
Psoriasis Area and Severity Index *		5.0 (4.7)	3.4 (4.2)
Body surface area*		10.7 (12.5)	5.0 (12.0)
Type of psoriasis			
Plaque	77 (96.3)		
Guttate	1 (1.3)		
Pustular	2 (2.5)		
Presence of arthropathy	19 (23.8)		

* Skewed distribution
SD = standard deviation
IQR = interquartile range

Table III: Differences in VCAT total score and subscales between the psoriasis patients and the control group(n=160)

Variable	Control (n=80)	Psoriasis (n=80)	Mean difference (95% CI)	t statistics (df)	p-value [a]
VCAT	25.94 (2.67)	25.38 (3.18)	0.56 (-0.35, 1.48)	1.21	0.227
VCAT memory	11.40 (1.31)	11.34 (1.53)			0.781
VCAT language	4.33 (0.79)	4.45 (0.83)			0.330
VCAT visuospatial	3.83 (0.38)	3.84 (0.37)			0.834
VCAT executive function	3.71 (1.43)	3.69 (1.44)			0.912
VCAT attention	2.67 (0.84)	2.06 (1.27)			<0.05

[a] Independent t test
CI = confidence interval
df = degree of freedom

Table IV: Association of psoriasis and psoriatic arthropathy with cognitive impairment risk measured using VCAT

Variable		Odd Ratio, OR	(95% CI OR)	χ2 stat. (df)[a]	p-value [a]
Psoriasis	Yes (n=80)	1.834	(0.845, 3.982)	2.408 (1)	0.125
	No (n=80)	1			
Psoriasis Arthropathy	Yes (n=19)	1.415	(0.458, 4.379)	0.356 (1)	0.547
	No (n=61)	1			

OR = odd ratio
CI = confidence interval
df = degree of freedom

Table V: Simple linear regression analysis on the VCAT and other clinical parameters

Independent Variable	b (95% CI β)	t statistics	r	r2	p-value
Psoriasis Area and Severity Index	0.046 (-0.105, 0.197)	0.606	0.068	0.005	0.546
Duration of psoriasis	-0.066 (-0.131, 0.000024)	-1.990	0.22	0.048	0.050

b = VCAT unit score
r = correlation coefficient
r^2 = coefficient of determination

observed in 17.5% and 21.3% of the control and psoriasis groups, respectively. Dyslipidaemia affected 45.0% of the control group and 37.5% of the psoriasis group.

Table II summarizes the disease characteristics among the psoriasis patients. Within the psoriasis group, the mean age of disease onset was 32.5 years, with an average disease duration of 11.6 years. The severity of psoriasis, as measured by the PASI, had a mean score of 5.0, and the mean BSA affected was 10.7%. Plaque psoriasis was the most common type, affecting 96.3% of patients, with smaller proportions presenting with pustular (2.5%) and guttate (1.3%) forms. Additionally, 23.8% of the psoriasis patients had psoriatic arthropathy, indicating joint involvement in a significant subset of patients.

Cognitive function was assessed using the VCAT across both groups, as shown in Table III. The overall VCAT scores did not differ significantly between the psoriasis and control groups, with mean scores of 25.38 (SD = 3.18) and 25.94 (SD = 2.67), respectively (p = 0.227). However, a closer examination of the VCAT sub-scores revealed a significantly lower score in the attention domain for psoriasis patients ($p < 0.05$), suggesting a possible association between psoriasis and specific cognitive impairments, particularly in attention.

The analysis of the association between psoriasis and cognitive impairment, presented in Table IV, did not reveal a statistically significant relationship. The odds ratio for cognitive impairment in psoriasis patients was 1.834 (95% CI: 0.845-3.982) with a p-value of 0.125, indicating that psoriasis alone may not be a strong predictor of cognitive impairment. Similarly, the presence of psoriatic arthropathy did not significantly increase the risk of cognitive impairment, with an odds ratio of 1.415 (95% CI: 0.458-4.379) and a p-value of 0.547.

Further investigation into the relationship between psoriasis severity, duration, and cognitive function was conducted using simple linear regression analysis, as shown in Table V. The analysis indicated no significant relationship between PASI scores and VCAT performance (p = 0.546, r = 0.068). However, there was a borderline significant negative association between the duration of psoriasis and VCAT scores (p = 0.05, r = 0.22), suggesting that prolonged psoriasis might be associated with a modest decline in cognitive performance. Although this finding suggests a potential impact of longer disease duration on cognitive function, the strength of the association was modest.

DISCUSSION

Demographics and disease characteristics

The demographic similarities between the psoriasis and control groups help ensure that the comparisons made in this study are not influenced by disparities in age and gender. This matching strengthens the validity of our findings. The disease characteristics such as age of onset, and psoriasis disease duration observed align with existing data from the Malaysian Psoriasis Registry.[18] However, the predominantly Malay composition of our sample, which differs slightly from the national registry, reflects the specific demographic makeup of the Kedah region.[19] The mean BSA involvement was 10.7%, and the mean PASI score was 5. In comparison, the Malaysian Psoriasis Registry reported a mean BSA involvement of 12.2% and a mean PASI score of 6.5 in adult psoriasis patients. These findings suggest that the patients in our study may have had a slightly lower disease severity than the broader population captured in the national registry.[18] Outpatient clinics typically manage patients with less severe forms of psoriasis, as those with more severe diseases are treated in inpatient settings. Consequently, the patient population in this study may have skewed towards those with slight milder disease.

Cognitive function comparison and association between psoriasis and psoriasis severity

The findings demonstrate that overall cognitive function, as measured by the VCAT, did not significantly differ between the psoriasis and control groups. Specifically, the mean VCAT score was 25.94 ± 2.67 for the control group and 25.38 ± 3.18 for the psoriasis group, with a p-value of 0.227. This suggests that psoriasis, despite being a chronic inflammatory condition, does not independently lead to significant cognitive impairment across most cognitive domains. There was significantly lower VCAT attention sub-score in the psoriasis group compared to the control group ($p < 0.05$). While the attention sub-score for psoriasis patients was lower, it is essential to consider that this assessment is based on a single question, which may limit the reliability of the finding. The significant difference might not robustly reflect a true cognitive deficit but could be an artifact of the limited assessment scope. This result underscores the need for more comprehensive tools to assess attention and other specific cognitive domains in future studies.[20]

The analysis of the association between psoriasis and cognitive impairment revealed an odds ratio of 1.834, with a p-value of 0.125. Although psoriasis patients showed a higher likelihood of cognitive impairment compared to controls, the result was not strong enough to confirm a definitive link. The PASI scores did not correlate significantly with VCAT scores (p = 0.546). This finding is consistent with previous studies,9 which reported similar results, reinforcing

the idea that cognitive impairment, when present, may be more closely related to the associated comorbidities or other factors rather than to psoriasis itself. It is noteworthy that metabolic syndrome, which is often associated with psoriasis,[21-23] has been significantly linked to cognitive impairment. This suggests that while psoriasis alone may not directly cause cognitive decline, the metabolic comorbidities frequently observed in psoriasis patients could contribute to the observed cognitive issues.[24-26] Additionally, the use of the VCAT in our study, compared to other studies that employed tools like the MMSE or MOCA, may have contributed to the negative findings regarding the association between psoriasis and cognitive impairment. VCAT is particularly advantageous in minimizing language-related biases, which can be a limitation in other cognitive assessments, thereby providing a more accurate evaluation of cognitive function across diverse populations.[12]

Psoriatic Arthropathy and Cognitive Function

There was no significant association found between the presence of psoriatic arthropathy and cognitive impairment ($p = 0.547$), contrasting with studies suggesting a link between psoriatic arthritis and cognitive impairment.[8,27] These studies highlight systemic inflammation, chronic pain, and longer disease duration as key contributors.[8,27] Systemic inflammation, a hallmark of psoriatic arthritis, has been suggested to drive neurodegenerative changes or vascular impairments that affect cognitive function.[8,27] Additionally, chronic pain and fatigue associated with psoriatic arthritis may create a mental burden that impairs attention and cognitive processing over time.[27] A possible reason for this discrepancy could be the very small sample size in this study ($n = 19$) compared to other studies[8,27] with larger sample sizes ($n = 96$ and $n = 117$, respectively), which have shown a positive relationship between psoriatic arthritis and cognitive impairment. The limited sample size in this study may have reduced the statistical power to detect such an association.[28]

Duration of Psoriasis and Cognitive Function

The relationship between the duration of psoriasis and cognitive function was found to be negatively associated, with longer disease duration correlating with lower VCAT scores ($p = 0.05$). This finding suggests that the cumulative burden of living with psoriasis over many years may contribute to a decline in cognitive function. However, the data do not provide strong evidence of a true association between psoriasis and cognitive impairment. When considering the overall VCAT scores and most subscales, there is no significant difference between psoriasis patients and controls, except for attention. This suggests that while there might be a potential association between psoriasis duration and cognitive function, it does not appear to be robust across different cognitive domains. Notably, other research has observed an association between psoriasis duration and cognitive impairment,[29] highlighting the need for larger sample sizes and longitudinal studies to better capture the potential long-term impact of psoriasis on cognitive function.

Limitations

This study has several limitations that must be considered. The sample size of 160 participants may be relatively small, which could limit the statistical power and generalizability of the findings. Additionally, the study population, predominantly Malay, may not represent the broader demographic diversity of psoriasis patients, restricting the applicability of the results to other ethnic groups. The use of the VCAT, while suitable for this population, may pose limitations in terms of comparability with other studies that utilize more widely validated cognitive assessment tools, such as the MoCA or MMSE. Furthermore, potential confounding factors, such as medication use and psychological stress, were not controlled for, which may influence cognitive outcomes independently of psoriasis. The cross-sectional design of the study limits the ability to establish causality between psoriasis and cognitive function, and the reliance on single-item measures for attention domains may reduce the reliability of specific findings. Lastly, the exclusion of certain comorbid conditions and the potential for selection bias in the control group further limit the study's generalizability and comparability.

CONCLUSION

While this study did not find broad cognitive impairment in psoriasis patients compared to controls, the specific deficit in attention and its association with the duration of psoriasis warrants further investigation. Understanding and addressing the cognitive aspects of psoriasis could significantly improve the overall quality of life for these patients.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS STATEMENT

Conceptualization – C.K.V, L.D.W. and K.K.K.; Methodology - C.K.V. and K.K.K.; Software - C.K.V. and K.K.K.; Data curation - C.K.V. and K.K.K.; Supervision – L.D.W.; Investigation - C.K.V.; Validation - C.K.V. and K.K.K.; Formal analysis - C.K.V.and K.K.K.; Visualization – C.K.V. and K.K.K.; Project administration - C.K.V.; Writing - original draft - C.K.V. and K.K.K.; Writing - review & editing - C.K.V., L.D.W. and K.K.K.

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Short-term outcome of hodgkin lymphoma patients and its prognostic factors in northeast peninsular Malaysia: A single centre experience

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ABSTRACT

Introduction: Hodgkin lymphoma (HL) is a hematopoietic malignancy characterized by the presence of Reed Sternberg cells, with generally favourable outcomes compared to other hematological malignancies. This study aims to determine the socio-demographic, clinical and treatment characteristics, as well as the short-term overall survival (OS) and progression-free survival (PFS) rates, of HL patients treated at Hospital Universiti Sains Malaysia (USM), a tertiary centre in northeast peninsular Malaysia.

Materials and Methods: We conducted a retrospective cohort study of HL patients treated from January 1, 2006, to December 31, 2018, with follow-up until December 31, 2021. Data on demographics, clinical features, treatments, and outcomes were analyzed. OS and PFS were estimated using the Kaplan-Meier method.

Results: Among 126 patients, the median follow up was 41 months. Most were male (55.6%) and of Malay ethnicity (97.6%). Nodular sclerosis was the predominant histology (52.4%), with 77.8% presenting with advanced-stage disease. All patients received chemotherapy, while 23.1% underwent combined modality therapy either with radiotherapy or immunotherapy. Post-treatment, only 34.1% achieved complete response. The 3-year OS and PFS rates were 74.9% and 59.5%, respectively—relatively lower than rates reported in developed countries. Independent adverse prognostic factors for OS and PFS included advanced-stage disease, bulky disease, elevated erythrocyte sedimentation rate.

Conclusion: This study highlights the need for tailored treatment approaches to improve HL outcomes in northeast Peninsular Malaysia. The relatively modest OS and PFS rates compared to developed nations suggest potential benefits from enhanced access to advanced therapied and diagnostic tools like positron emission tomography computed tomography (PET-CT) scan.

KEYWORDS:
Hodgkin lymphoma, Malaysia, treatment outcome, prognostic factors, survival

INTRODUCTION

Hodgkin lymphoma (HL) exhibits varied epidemiological patterns across gender, age, and geography. Its incidence follows a bimodal distribution, peaking in adolescence/young adulthood and later in individuals over 55-year-old.[1] In Malaysia, the highest incidence occurs between ages 25-29 and 70-74.[2]

HL classification, primarily divided into classical and nodular lymphocytes-predominant HL, guides treatment decisions. Furthermore, the Ann-Arbor staging system, supplemented by additional risk factors, aids in this process. Early-stage HL is often managed with combined modality therapy, whereas advanced-stage disease may necessitate escalated chemotherapy regimens. However, optimal treatment strategies continue to evolve especially for relapsed or refractory cases, in which highly active immunotherapies, such as brentuximab vedotin (an anti-CD30 monoclonal antibody), checkpoint inhibitors like nivolumab and pembrolizumab, along with high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT), emerge as a cornerstone.

Understanding the prevalence and treatment outcomes of HL, particularly in Malaysia, is vital for local clinical haematologists. Therefore, this study aims to investigate the short-term outcomes and prognostic factors among HL patients treated at a tertiary centre in northeast Peninsular Malaysia.

MATERIALS AND METHODS

This study was a retrospective cohort study involving a review of medical records of HL patients undergoing treatment and follow-up at Hospital Universiti Sains Malaysia (USM), a tertiary referral centre for haematological cases in northeast Peninsular Malaysia. Data were collected from the medical records of HL patients in the database registry between January 1, 2006, and December 31, 2018, with an additional follow-up period of three years from January 1, 2019, until December 31, 2021. Thus, the total duration of this retrospective observation window was 192 months. During the follow-up period, patients were monitored through

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scheduled clinical assessments, surveillance imaging studies, and laboratory evaluations. These measures were taken to assess treatment response, monitor for disease progression or relapse, and manage any treatment-related complications.

This study included patients diagnosed with HL within the specified period, aged over 12 years, who had received at least one cycle of induction chemotherapy after diagnosis. Patients with concurrent malignancy or another type of malignancy prior to the HL diagnosis, those who did not receive or refused any treatment during the study period, and those missing baseline evaluations for more than three variables were excluded. At Hospital USM, 138 HL patients were treated between January 1, 2006, and December 31, 2018, with 126 patients meeting the eligibility criteria. Therefore, no sampling method was applied, and all eligible patients were included in the study.

Data were entered and analysed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0. For categorical variables, the frequency of observations and percentages were calculated. Survival analysis was chosen as the statistical test because the research objectives included time to an event i.e., death or relapse/progression of HL. Overall survival (OS) was defined as the duration from the date of diagnosis to the date of death. The event for survival time was death among HL patients during the study period, regardless of the cause of death. The censored observation for OS were either patients alive at the closure of the study or those lost to follow-up during the study period.

Progression-free survival (PFS) was defined as the duration from the date of diagnosis until the date of disease relapse/progression. The event of the study was the time to disease relapse/progression. The censored observation for PFS were either patients who achieved complete response (CR) at the closure of the study or those lost to follow-up during the study period.

A simple Cox proportional hazards model was conducted on selected independent variables to provide a preliminary idea of potential prognostic importance ($p<0.25$). The significant level was obtained from the Wald statistic. Subsequently, a multiple Cox proportional hazards model was used to identify prognostic factors for death and disease relapse/progression associated with OS and PFS. Two statistical analyses were executed for variables with a p-value less than 0.25 in univariate Cox regression analysis: forward stepwise (Wald) and backward stepwise (Wald). The second analysis included all independent variables in the model based on their statistical significance. The final model with adjusted hazard ratio (HR) and 95% confidence interval, Wald statistic and corresponding p-value were presented. A p-value less than 0.05 was considered statistically significant.

RESULTS

Among the 126 patients with HL, there was a slight male predominance, with 70 males (55.6%) and 56 females (44.4%). The median age was 28 years (range 12-78 years). Most patients were under 45 years old (84.9%) and predominantly Malay (97.6%).

Majority of patients presented with B symptoms (n=68, 54%) and nodal involvement (n=103, 81.7%). Biopsy-proven extra nodal involvement was identified in specific sites, including the bone marrow in 17 patients, the lungs in 5 patients, and the spleen in 1 patient. The most common histologic subtypes were nodular sclerosis (n=66, 52.4%), followed by mixed cellularity (n=35, 27.8%) and unclassified (n=11, 8.7%). Elevated LDH and ESR at diagnosis were recorded in 40.5% and 48.4% of patients, respectively. Among these patients, 98 patients (77.8%) had advanced-stage disease (stage III-IV) at presentation (Table I). Staging was based on the Ann Arbor staging system, which categorizes disease extent into stages I-IV, with further classifications based on symptoms (A or B) and bulk of disease.

The treatment characteristics are presented in Table II. Sixty-two patients (49.2%) received front-line treatment within four weeks of diagnosis. Majority of HL patients received first-line treatment with the ABVD protocol (doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine) (n=121, 96%). More than half of the patients received one line of treatment (n=67, 53.2%), while 59 patients (46.8%) received two or more lines of treatment. In term of treatment modality, 97 patients (77.0%) received chemotherapy alone, 23 patients (18.3%) received chemo-radiotherapy, and 6 patients (4.8%) received chemo-immunotherapy. About 17.5% of patients (n=22) underwent HDC plus ASCT. Of the 22 transplanted patients, six received brentuximab vedotin during salvage therapy and/or as maintenance therapy.

Among the 126 patients treated, response data was available in 87% of patients either via contrast-enhanced computed tomography (CECT) scan or positron emission tomography computed tomography (PET-CT) scan. In a centre without in-house PET-CT service, 78 patients (61.9%) underwent end-of-treatment (EOT) PET-CT scans, while 32 patients (25.4%) underwent EOT CECT scan. The complete response (CR) rate was 34.1%, partial response (PR) was 26.2%, while stable disease (SD) and progressive disease (PD) were 7% and 22.6%, respectively, after first-line treatment. We assessed treatment response according to the 2007 Cheson criteria for lymphoma, defining CR as the disappearance of all evidence of disease and PR as ≥50% reduction in tumour burden, after completing first-line treatment.

With a median follow-up of 41 months, the 1-year and 3-year OS were 91.7% and 74.9%. Meanwhile, the 1-year and 3-year PFS were 83.4% and 59.5%, respectively (Figure 1). Various potential prognostic factors were evaluated using simple Cox proportional hazards regression to identify possible significant independent prognostic factors for death in HL patients. There factors included the presence of bulky disease ($p=0.023$), extranodal involvement ($p=0.175$), staging ($p=0.037$), elevated ESR ($p=0.006$), and elevated LDH ($p=0.053$) at diagnosis. These variables (with a p-value < 0.25) were then included in the multiple Cox regression analysis. Only two prognostic factors were found to be significant independent predictors of mortality among HL patients. Patients with bulky disease had a 1.9 times higher hazard of death compared to those without bulky disease ($p= 0.041$). Additionally, patients with elevated ESR had a 2.2-fold higher risk of dying ($p=0.018$) (Table III).

Table I: Baseline characteristics of the patients (n=126)

Baseline characteristics	Frequency (n)	Percentage (%)
B symptoms		
Yes	68	54.0
No	58	46.0
Bulky disease		
Yes	41	32.5
No	85	67.5
Elevated LDH at diagnosis (IU/L)		
Yes (≥500)	51	40.5
No (<500)	75	59.5
Extranodal involvement		
Yes	23	18.3
No	103	81.7
Elevated ESR at diagnosisa (mm/hr)		
Yes (>50)	59	48.4
No (≤50)	63	51.6
Histologic Subtypes		
Classical HL		
Nodular sclerosing	66	52.4
Mixed cellularity	35	27.8
Lymphocytes rich	6	4.8
Lymphocytes depleted	1	0.8
Unclassified	11	8.7
Non-Classical HL		
Nodular lymphocytes predominant	7	5.6
Stage of disease		
I	3	2.4
IIA	25	19.8
IIB	10	7.9
III	37	29.4
IV	51	40.5
Early stage	28	22.2
Advanced stage	98	77.8

[a]Missing data, n =4
n=frequency; %=percentage; SD=standard deviation
ESR, erythrocytes sedimentation rate; LDH, lactate dehydrogenase
Early stage: (I-IIA); Advanced stage: (II with bulky disease, III, IV)
HL, Hodgkin lymphoma

Table II: Treatment characteristics of the HL patients (n=126)

Treatment Characteristics	Frequency (n)	Percentage (%)
Time from diagnosis to treatment (TDT)		
≤ 4 weeks	62	49.2
5-8 weeks	29	23.0
>8 weeks	35	27.8
Line of treatment		
One line of treatment	67	53.2
≥ 2 lines of treatment	59	46.8
Treatment modalities		
Combination chemotherapy alone	97	77.0
Chemo-radiotherapy	23	18.3
Chemo-immunotherapy	6	4.8
Received HDC with ASCT		
Yes	22	17.5
No	104	82.5

Descriptive statistics
n=frequency; %=percentage
HDC, high dose chemotherapy
ASCT, autologous stem cell transplantation
HL, Hodgkin lymphoma

Table III: Prognostic factors of death by using multiple Cox proportional hazards regression model (n=126)

Variables	b	Adjusted HR[a] (95% CI)	Wald statistic	p-value
Bulky disease				
No	0	1	4.169	0.041
Yes	0.662	1.938(1.027,3.657)		
Elevated ESR[b]				
No	0	1	5.580	0.018
Yes	0.795	2.215(1.145,4.285)		

[a]Backward likelihood ratio multivariate cox proportional hazard regression [b]Missing data n=4
b, Regression coefficient; HR, hazard ratio; CI, Confidence Interval
ESR, erythrocyte sedimentation rate

Table IV: Prognostic factors of relapse/disease progression by multiple Cox proportional hazards regression model (n=126)

Variables	b	Adjusted HR[a] (95% CI)	Wald statistic	p-value
Bulky disease				
No	0	1	8.233	0.004
Yes	0.877	2.404(1.320,4.377)		
Elevated ESR[b]				
No	0	1	4.175	0.041
Yes	0.637	1.892(1.026,3.487)		

[a]Backward likelihood ratio multivariate cox proportional hazard regression [b]Missing data n=4
b, Regression coefficient; HR, hazard ratio; CI, Confidence Interval
ESR, erythrocyte sedimentation rate
p-value < 0.05 is significant

Similarly, the presence of bulky disease (p<0.001), extranodal involvement (p=0.031), elevated ESR (p=0.004), staging (p=0.005), and treatment modality (p=0.039) were potential prognostic factors for disease relapse/progression via simple Cox proportional hazards regression. In multiple Cox regression analysis, two variables were identified as significant prognostic factors for disease relapse/progression: the presence of bulky disease (p=0.004) and elevated ESR (p=0.041) (Table 4). Notably, there was a 2.4 times increased risk of relapse/progressive disease in the presence of bulky disease, and 1.89 times increased risk in HL patients with elevated ESR.

DISCUSSION

Our study reported that the median age at presentation was 28 years, with a slight male preponderance. Majority of patients had classical HL with nodular sclerosis being the most common subtype (52.4%), followed by mixed cellularity subtype (27.8%). The overall age, gender, and HL subtype distribution resembled a previous study in Malaysia.[3] However, our data contradicted results from several studies in developing countries including in Africa and India, where the mixed cellularity HL subtype was reported to be the predominant.[4,5]

More than two-thirds of patients were diagnosed with advanced-stage disease (98 patients, 77.8%), with stage IV (51 patients, 40.4%) being the most frequently encountered. These findings corresponded with previous studies in developing countries.[6,7] In contrast, more than half of HL patients in a retrospective study in Johor, Malaysia and in Iraq presented with stage II disease.[3,8]

Our study revealed 1-year and 3-year OS rates of 91.7% and 74.9%, respectively, and 1-year and 3-year PFS rates of 83.4% and 59.5%, respectively. These figures are comparable to previous studies in India, which reported 5-year OS and PFS rates of 60% and 58%, respectively.[9] However, our figures are significantly lower than those observed in developed countries, especially for advanced-stage disease. Recent studies by Radford et al. and Johnson et al. reported higher 3-year OS rates of 99.0% and 95.8% in early and advanced stages, respectively.[10,11] Another study in Saudi Arabia also reported better survival with 3-year and 5-year OS rates of 93.0% and 91.0%, respectively.[7]

Our study demonstrated that older patients (> 45 years) had lower survival rates compared to the younger age group. This finding corresponds with another study that found younger age groups had greater survival rates across all stages of HL.[12] A study in the United States reported that patients aged 45 or older had a higher hazard ratio of 5.25 for mortality.[13] Several factors could explain why older people had lower survival rates than younger age groups, including the presence of co-morbidities, poor organ function and therefore, increased susceptibility to treatment-related toxicities and poor treatment tolerance.[14] Additionally, older people are associated with a higher frequency of mixed cellularity subtypes compared to younger age groups (nodular sclerosing subtypes) and often present with advanced stages of HL.[15]

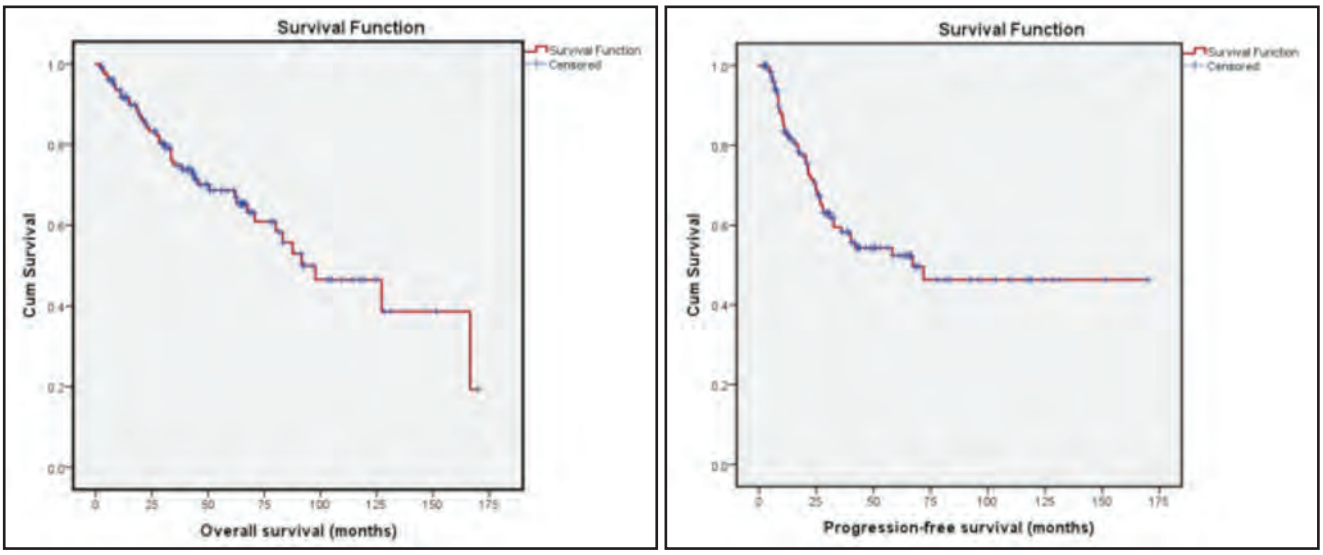

Fig. 1: Kaplan-Meier survival curve for 1-year and 3-year overall survival & 1-year & 3-year progression-free survival in HL patients in Hospital USM

In general, early initiation of combination chemotherapy alone or combined modality therapy provides better survival compared to patients without any treatment. However, in this study, there was no significant correlation between the time from diagnosis to treatment initiation (TDT), and OS and PFS. In a study by Brooks et al., investigating 810 patients with classical HL treated with ABVD, the 5-year OS was 92% for TDT <4 weeks, 92% for TDT 5–8 weeks, and 83% for TDT > 8 weeks (p=0.007).[16] This is an area of interest that we would like to explore, as patient refusal for treatment following a cancer diagnosis remains a significant issue.

Our study demonstrates that bulky disease and high ESR are two significant prognostic factors for death and disease relapse/progression among our HL patients. This finding aligns with previous studies that highlighted the influence of bulky disease and high ESR on patient survival, in addition to factors like high LDH, low albumin level, poor performance status and B symptoms.[17,18]

Several factors might have contributed to the low survival of our HL patients. Late presentation leading to advanced stage at diagnosis, difficult access to novel medications for salvage treatment such as highly active immunotherapy and checkpoint inhibitors, and most importantly, difficult access to PET-CT scans for staging and interim assessments make it challenging to adapt treatment escalation or de-escalation and decide on incorporating combined-modality treatment (chemo-radiotherapy). The use of early (interim) PET-CT scan for early treatment adaptation has significantly improved survival in HL patients.[19]

In relapse refractory setting, only small proportions of our patient received effective salvage therapy using novel agent modalities such as immunotherapy or check point inhibitor, mainly due to cost issue. This reflect the small proportion of our patients who were chemo sensitive able to undergo HDC plus ASCT.

For patients with relapsed or refractory HL who do not respond adequately to standard therapies, allogeneic stem cell transplantation (allo-SCT) may be considered. However, none of our patients were able to undergo this procedure due to its complexity. Although allo-SCT offers the potential for long-term remission, it is associated with significant risks, including graft-versus-host-disease, and increased transplant-related mortality, making careful patient selection essential.

CONCLUSION

This study provides a comprehensive analysis of the short-term outcomes and prognostic factors of HL in northeast Peninsular Malaysia, highlighting significant findings such as the predominance of nodular sclerosis subtype and the high prevalence of advances-stage disease at presentation. We observed relatively modest OS and PFS rates compared with those reported in more developed nations, with advanced-stage disease, bulky disease, and elevated ESR identified as significant adverse prognostic factors. These findings highlight the need for tailored treatment strategies that consider these risk factors and emphasize the importance of timely access to advanced diagnostic tools, such as PET-CT, to improve patient outcomes. Moving forward, longer-term studies are essential to refine treatment protocols, address the challenges of relapse and refractory cases, and enhance survival rates for patients in this setting.

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ETHICAL CONSIDERATIONS

This study adhered to the ethical guidelines established by the 18th World Medical Assembly (Helsinki, 1964), including all subsequent revisions. Patient identities and clinical data were treated with strict confidentiality, reported only in aggregate form without personal identifiers. Approval for the study was granted by the USM Ethics Committee under JEPeM Code: USM/JEPeM/22010077 on March 13, 2022.

CONFLICT OF INTEREST

None

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Empathy and listening style among occupational therapists in Malaysia

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ABSTRACT

Introduction: As an occupational therapist, listening and empathy are critical components of practice because they are the foundation for developing therapeutic rapport with patients and their relatives. Currently, there is still no study regarding the level of empathy and listening styles among Occupational therapists in Malaysia. This study investigates the level of empathy and listening styles among occupational therapists in Malaysia and to examine their correlations.

Materials and Methods: A cross-sectional study was conducted with 244 occupational therapy practitioners; 43 males; and 181 females. The level of empathy and listening style were assessed using the Jefferson Scale of Empathy Health Professional version and Listening Styles Profile-Revised questionnaires. Data were collected using Google Form. Analysis data were done using IBM SPSS Statistical Software version 26.

Results: Statistical analysis showed that Malaysia occupational therapists preferred perspective taking (mean 55.67, Standard Deviation, SD 10.54) in empathy and the analytical listening in listening styles approach (mean 34.71, SD 6.76). In addition, there was a moderate to strong significant correlation between the level of empathy and listening styles (r = 0.419 to 0.648, p<0.05). Furthermore, there is significant difference between listening styles and empathy in relation to gender (male>female) p=0.001-0.038), race (Indian higher than Malay and Chinese) and areas of practice (paediatric higher than psychiatric) (p= 0.016 to 0.039).

Conclusion: The findings are helpful for occupational therapists to improve their quality services by being more listening and empathetic while providing proper intervention to the patients.

KEYWORDS:
Empathy, listening styles, occupational therapist, Jefferson Scale of Empathy, listening styles profile-revised

INTRODUCTION

Empathy is an essential skill for health care practitioners.[1,2] Empathy-related emotional intelligence has been shown to enhance several elements of healthcare practice. These include patient satisfaction, adherence to therapy, history-taking and diagnosis, resource use, and a decrease in patient lawsuits.[3] Empathy in patient care is defined as the ability to understand what a patient is saying and experiencing and then verbally communicate this comprehension to the patient.[2,3] Empathy is crucial for occupational therapists because it helps them focus on their patients' needs rather than their own to achieve the most beneficial occupational and therapeutic results possible for their patients.[4]

Two studies found that there is no evidence of different age affect a person's empathy style.[5,6] Moreover, a study involving a large sample of persons aged 16 to 87 years old found no significant age differences in self-reported empathy.[5] In addition, other study also found no significant age differences in empathy in a sample ranging from 15 to 87 years.[6] However, other factors such as gender, professional aspirations, current course of study, family structure and environment, personality, and empathetic experiences are likely to influence empathy.[7] Numerous studies have shown evidence that contradicts the widely held belief that women are more compassionate than males.[8-10]

Watson et al.,[11] defined listening as attitudes, beliefs, and distortions that constitute an individual's overall preference towards the how, where, when, who, and what of information intake and encoding. The study stated that occupational therapists could understand and explore client problem and give them the strength to deal with it, by listening to patients.[12] Listening is crucial to occupational therapy because it contributes to people's happiness.

Listening style refers to the method a person uses when listening, whereas attentive manner refers to the subject a person focuses on when listening. Good listening and communication positively impact the formation of health professional and patient relationships, improving patient knowledge, adherence to treatment routines, and patient satisfaction.

A skilled occupational therapist must demonstrate empathy and attentive listening while attending to a patient. Occupational therapists must visualise their clients in various roles and circumstances to tailor treatments to each client's particular goals.[13] Effective listening and empathic

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communication have beneficial effects on establishing healthcare provider-patient relationships, patient comprehension, treatment program adherence, and satisfaction levels.[14]

However, the information about empathy and listening style among occupational therapists in Malaysia is still unexplored. To date, there are no studies looking at empathy and listening styles among occupational therapists in Malaysia. Therefore, the aim of this study investigates the level of empathy and listening styles, as well as the association between empathy and listening styles among occupational therapists in Malaysia.

MATERIALS AND METHODS

Study Design

The study is a cross-sectional survey of occupational therapy practitioners in Malaysia.

Study Instruments

A questionnaire form was used as an instrument to collect data on empathy and listening styles. Data were collected using the standardised self-reporting questionnaires; Jefferson Scale of Empathy Health Professional version (JSE-HP)[15] and Listening Styles Profile-Revised (LSP-R)[16] questionnaires. Permission has been obtained from both main authors. The JSPE [15], and LSP-R 16 has proven to be reliable and valid. Both item-total score correlations were positive and statistically significant ($p < 0.01$), and Cronbach alpha < 0.82.[15,16,17]

Sample size

A total of 1892 occupational therapy practitioners were identified from registered occupational therapists at Malaysia Occupational Therapist Association (MOTA, 2022) . The Raosoft online calculator was used to calculate the sample size. Consideration margin of error 5%, confident level 95%, and response distribution rate 50%. The recommended sample size is n=385. All occupational therapy practitioners working in government and private sectors in Malaysia were included in this study.

Procedures

Questionnaires were distributed using Google Form. It consists of questions on demographic profile, i.e., age, gender, place of practice, and work area; and the JSE-HP and LSP-R for assessing empathy and listening styles.

Statistical Analysis

Data were analysed using IBM SPSS Statistical Software version 26. Normality testing was conducted to determine proper statistical testing (i.e., parametric or non-parametric) for the demographic and the scores obtained from the participants. The Kolmogorov test was performed for the normality test because the sample size for this study is smaller than 100. The relationship between empathy and listening styles was conducted by Spearman correlation (rho). Spearman rank correlation is a non-parametric test used to measure the degree of association between two variables. Spearman correlation was also computed to examine the relationship between an occupational therapist's demographic factors (age and work experiences) and their empathy and listening styles. A Kruskal-Wallis test was conducted to compare the listening styles and empathy with demographic data (gender, race, work area, and area of practice).

RESULTS

Number of Participants

The questionnaire was distributed to all 1892 occupational therapy practitioners. However, only a 11.84 % (n=224) returned the questionnaire. The participants came from all the fifteen states in Malaysia. The highest number of participants came from Johor (29.0%). Perlis and WP Putrajaya had the lowest participant number (0.9%). There were more female compared to male participants in all states. All occupational therapists from the private sector (2.2%) have a degree in occupational therapists and earns an income equivalent to grade U41 in the government sector.

Table I shows the participants' demographic characteristics. The participants age between 23 and 58 years old, with a mean age of 32.71(SD=5.3) years. The majority of the participants was female (80.8%), Malays (79.5%) and works as occupational therapists (88.4%).

Participants' preference of the Listening Styles in the LSP-R

The Listening Styles Profile-Revised (LSP-R) consists of 24-item. All the items were randomised before administration. Items 1,5,9,13,17 and 21 are for Relational Listening (RL), and items 2,6,10,14,18, and 22 are for Analytical Listening (AL). Task-Oriented Listening (TL) represents items 3,7,11,15,19, and 23 while critical listening (CL) represents items 4,8,12,16,20, and 24. As for the result, Table II shows the participants' most preference in their listening styles is the Analytical Listening styles (AL) (M=34.71, SD=6.76) and the least is Task-oriented Listening (M=27.98, SD=7.82).

Participants' preference of the Empathy in the JSE-HP

There are 20-item in JSE-HP. It was designed specifically for administration to health professions students and practitioners to evaluate empathy in the context of health professions education and patient care. The subscales factors are Perspective Taking (PT), Compassionate care (CC), and Walking in Patient's Shoes (PS). All the items were randomised before administration. Items 2,4,5,9,10,13,15,16,17 and 20 are for Compassionate care (CC), and items 3 and 6 are for Walking in Patient's Shoes (PS). The items were graded on a 7-point Likert scale (1=Strongly Disagree, 7=Strongly Agree). The results vary from a minimum of 20 to a maximum of 140. A higher score means a more empathic person. As for the result, Table II shows the participants' most preference in their empathy is Perspective Taking (M=55.67, SD=10.54); Compassionate Care (M=28.47, SD=10.37), and the least is walking in the patient's shoes (M=7.56, SD=2.86).

Correlation between Empathy and Listening Styles with Demographic Factors

The results in Table III shows a moderate correlation and significance between empathy and listening styles which are Perspective taking and Relational Listening (r = 0.679);

Table I: Participants' Demographic Characteristics

Characteristics	n	%
Gender		
Male	43	19.2
Female*	181	80.8
Race		
Malay*	178	79.5
Chinese	6	2.7
Indian	7	3.1
Others	33	14.7
Education level		
Diploma*	157	70.1
Bachelor's Degree	60	26.8
Master's Degree	7	3.1
Income		
RM 2000- RM 3999*	144	64.3
RM 4000- RM 5999	75	33.5
RM 6000- RM 7999	4	1.8
RM 8000 - RM 9999	1	0.4
Work setting		
Hospital*	173	77.2
Private sector	5	2.2
Clinic	38	17.0
Other	8	3.6
Position in Clinical setting		
occupational therapists *	198	88.4
occupational therapists' officer	26	11.6
Grade		
U29*	151	67.4
U32	45	20.1
U36	1	0.4
U38	2	0.9
U41	16	7.1
U44	9	4.0
Area Practice		
Paediatric	72	32.1
Psychiatric	40	17.9
Physical dysfunction*	112	50.0

Note: (*) indicated the highest

Table II: Analysis of the listening styles in the LSP-R and empathy score in each of the three factors of JSE

Listening styles	Mean	SD
Relational Listening	33.82	6.70
Analytical listening*	34.71*	6.76
Task-Oriented Listening	27.98	7.82
Critical Listening	29.07	6.49
Empathy score (Subscales)		
Perspective Taking*	55.67	10.54
Compassionate Care	28.47	10.37
Walking in Patient's Shoes	7.56	2.86

Note: (*) indicated the highest, SD – standard deviation.

Table IV: Correlation between occupational therapists' demographic factors and their empathy and listening styles.

Variables	Age	Work Experience
Relational listening (RL)	0.123	0.106
Analytical Listening (AL)	0.083	0.055
Task-Oriented Listening (TL)	0.039	-0.013
Critical Listening (CL)	0.000	-0.062
Perspective Taking (PT)	0.113	0.42
Compassionate Care (CC)	0.061	0.017
Walking in Patient's Shoes (PS)	0.050	-0.033

Table V: The significant differences between listening styles and empathy with the demographic data

Domain	Groups	Mean	H	P
	Gender			
Analytical Listening	Male	140.69*	10.145	0.001*
	Female	105.80		
Perspective Taking	Male	131.87*	4.492	0.034*
	Female	108.14		
Compassionate Care	Male	130.87*	4.285	0.038*
	Female	108.14		
	Race			
Relational Listening	Malay	106.35	10.536	0.015*
	Chinese	141.75		
	Indian	171.36*		
	Other	127.89		
Perspective Taking	Malay	105.31	11.112	0.011*
	Chinese	124.75		
	Indian	145.71*		
	Other	142.00		
	Area of practice			
Critical Listening	Pediatric	126.52	8.272	0.016*
	Psychiatric	89.95		
	Physical dysfunction	111.54		
Compassionate Care	Pediatric	123.02	6.482	0.039*
	Psychiatric	124.38		
	Physical dysfunction	101.50		
	Work Area setting			
Walking in Patient's Shoes	Hospital	115.88	9.195	0.027*
	Private	108.90		
	Clinic	88.63		
	Other	154.94*		

*Statistically significant difference

Perspective taking and Analytical Listening (r = 0.648); Compassionate Care and Critical Listening (r = 0.444) and Perspective taking and critical listening (r = 0.419).

Spearman correlation analysis was computed to examine the relationship between an occupational therapist's demographic factors (age and work experiences) and their empathy and listening styles. Table IV shows a correlation between age and work experience with empathy and listening styles among occupational therapists. Based on the result of this study, there is a low association between an occupational therapist's demographic factors (age and work experiences) and their empathy and listening.

There was a statistically significant difference between Listening styles and empathy in relation to gender (p=0.001 to 0.038), race (p=0.015 to 0.011), and area of practice (p=0.016 to 0.039). However, in empathy only Walking in Patient's Shoes was found statistically significant in relation to work area (H= 9.195, p=0.027) (Table V).

DISCUSSION

Mostly occupational therapists in Malaysia preferred analytical listening styles with patients. However, in empathy they preferred the factor that has therapeutic value. Malaysia Occupational therapists preferred perspective taking in empathy. This is where, perspective taking is a cognitive-based intervention that promotes another focus by directing one to imagine how a person's suffering affects that person's life. [18] All three studies by Blatt et al.,[14] show patients' increased satisfaction when giving perspective taking intervention. Perspective taking as a means of improving patient satisfaction deserves further exploration in clinical training and practice. It has been shown to increase empathy, help, and neural level responses to others' pain, thus promoting positive intergroup attitudes.[19]

Occupational therapists in Malaysia preferred analytical listening as a listening style during conducting sessions and implying empathy with patients. Thus, information verified that occupational therapists background in healthcare is linked to analytical listening. Analytical listening is also suitable for getting complex information. This showed that occupational therapists act assertively when there were misunderstandings occur. They also pay attention in interactions by asking clarifying questions to form objective opinions.[20] In addition, Villaume and Bodie[21] reported that there was a link between analytical listening, open communication, and accurate argumentation about conversational information. Moreover, analytical listeners can check information to reduce medical interpretation mistakes because they need to think and handle complex information. Hence, analytical listening should ensure correct information during a medical consultation.

There is no correlation between occupational therapists' demographic factors (age and work experiences) with their empathy and listening styles. This study confirmed with the other two studies where no evidence of age variations in empathy.[5,6] In contrary, three studies reported of negative age differences.[22,23] According to Phillips[23], young adults reported

higher empathy than older adults. However, once education was factored in, the age impact was no longer significant, they suggested that age-related variations in empathy were mainly due to age differences in education. Furthermore, Schieman[19] identified a negative relationship between age and self-reported empathy among 1581 persons (aged 22 to 92). Nevertheless, the negative association between age and empathy remained significant even after adjusting for several sociodemographic, health-related, and psychological factors.

Occupational therapists in Malaysia have significant difference between empathy and listening styles in relation with gender (male higher than female), race (Indian higher than Malay and Chinese), and area of practice (paediatric higher than psychiatric). This study refuted by Maccoby and Jackling[23] findings, where females outperform males in verbal memory, listening to nonverbal behaviours such as facial expression, especially when exposed to both visual and auditory stimuli[23], and in perceiving gender-related traits. Moreover, empathy is probably influenced by various factors, including gender, intention to pursue a future career, the current course of study, family structure and environment, personality, and empathetic experiences.[7] Furthermore, it can also be influenced by the socio-cultural, socio-cultural environment and, the scale of ethical.8,20 Different cultural characteristics of the participants also appear to influence their listening effectiveness. For example, Kiewitz et al.,[15] found that various cultural traits affect participants' listening effectiveness. They reported that Americans pay close attention to a speaker's feelings, Israelis pay attention to the accuracy of the information, and Germans participate in oral communication by interrupting with questions as the speaker talks.

The outcomes of this study are helpful for occupational therapists to improve quality services by being more listening and empathetic while providing proper assessment and intervention to the patient. Besides, this study can embrace the core concepts of occupational therapists' attitudes toward giving patient services. This study's implication would interest scholars in occupational therapy and practicing students for highlighting empathy and proper listening while handling patients. However, there many limitations in this study. First, the sample size not within the ideal sample size. Second, random sampling could not be done, thus can affect the ideal representatives among area of practice. Third, the questionnaires should be translated into Malay language so that it is easily understood among occupational therapists' study background in Malay medium language.

CONCLUSION

This study provided information regarding empathy and listening styles among occupational therapists in Malaysia and insights into factors that influenced the empathy and listening styles among occupational therapists in Malaysia. Furthermore, the result of this study indicates Malaysian occupational therapists need to improve quality services by being more listening and empathetic while providing proper assessment and intervention to the patient. Besides, this study can embrace the core concepts of occupational therapists' attitudes toward giving patient services. This study's implication would be of interest to scholars in occupational therapy as well as to practicing student for highlighting empathy and proper listening while handling patients. However, this study only identifies baseline empathy and listening styles among occupational therapists in Malaysia. More study needed especially introducing causal effect that can improve empathy and listening styles among occupational therapists or other health professional in Malaysia.

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ETHICS APPROVAL AND INFPRMED CONSENT

The Research Ethics Committee (REC), Institute of Research Management and Innovation (IRMI), Universiti Teknologi MARA, Shah Alam, Selangor approved this study: 500-FSK (PT. 23/4).

CONFLICT OF INTEREST

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AUTHORS CONTRIBUTION

Conceptualisation: NA, MSM; data curation and formal analysis: NA, MSM; Methodology: NA, MSM, II; writing original draft: NA, MSM; writing review and editing: NA, MSM, SNZ, UA.

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Prognostic factors of the survival of pancreatic cancer patients in peninsular Malaysia: A survival analysis

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ABSTRACT

Introduction: Pancreatic cancer incidence in Malaysia is steadily on the rise, now ranking as the 14th most common malignancy in the country. Despite this upward trend, research on prognostic factors affecting pancreatic cancer survival remains limited, highlighting the need for ongoing investigation to improve patient survival outcomes.

Materials and Methods: This study was conducted retrospectively by reviewing records of pancreatic cancer patients hospitalized between January 2011 and December 2018 across multiple health centres in Malaysia. Using Cox proportional hazards regression analysis, several prognostic factors were identified.

Results: The study revealed that being Chinese, having a family history of pancreatic cancer, having hepatitis C, presenting with jaundice, experiencing pale stools, having a palpable mass in the abdomen, the presence of ascites, receiving palliative care and end-of-life care were associated with higher mortality risk. Conversely, being female, having hypertension, and higher haemoglobin levels were linked to decreased mortality risk.

Conclusions: These study findings offer valuable insights into prognostic factors for predicting patient outcomes and optimizing individual prognosis in pancreatic cancer cases within Malaysia context. Future research should build on these findings, exploring how these factors can be integrated into comprehensive care plans that address the specific needs of diverse patient populations.

KEYWORDS:
Pancreatic cancer, prognostic factors, Cox regression, survival, Malaysia, retrospective record review

INTRODUCTION

Pancreatic cancer has become as an emerging non-communicable disease, manifesting a gradual escalation in its incidence over recent years. Currently ranked as the 12th most common oncological disease globally,[1] its prevalence is rising by 1.1% annually.[2] Understanding its potential risk factors and recognizing its signs and symptoms are of ultimate importance for primary prevention and early diagnosis of the disease. However, pancreatic cancer is often clinically silent, and patients are frequently diagnosed at advanced stages. Consequently, its survival rate is exceedingly low compared to other malignancies.[3] In the year 2020, the disease was responsible for 466,003 global fatalities,[4] nearly matching the number of new cases annually.[2] Pancreatic cancer fatalities contribute to 4.7% of all global cancer-related deaths, making it the seventh leading cause of cancer mortality among all oncological diseases.[4]

Prognosis in pancreatic cancer patients depends on several factors. Prognostic factors are variables that indicate which patients are likely to do better or worse over time. Data on prognostic factors provide insights on the natural history of a disease, and these data are crucial to predict patients' probable outcomes and optimise patient individual's prognosis.[5] In Malaysia, the incidence of pancreatic carcinoma is on the rise, with reported cases increasing from 976 in 2018[6] to 1089 in 2020,[7] representing the 14th most common malignancy in the country.[7] Despite this upward trend, research on prognostic factors affecting survival of pancreatic cancer patients in Malaysia remains limited. A comprehensive understanding and identification of these factors are imperative for effective management. To date, the prognostic factors of pancreatic carcinoma are still insufficiently known. Therefore, ongoing research aimed at elucidating prognostic factors and improving survival rates for pancreatic cancer patients is essential. This study aims to provide further insights into the influencing factors on the overall survival of pancreatic cancer patients through a multicentre retrospective cohort study in Malaysia.

MATERIALS AND METHODS

A retrospective cohort study was conducted by comprehensively reviewing the medical records pertaining to pancreatic cancer patients aged 18 years and above, who were admitted to State hospitals in Terengganu, Kelantan, Penang, and Kedah between January 2011 and December 2018. Inclusion criteria encompassed patients with confirmed pancreatic cancer diagnoses, established through histopathology examination or various diagnostic imaging modalities. Patients with incomplete medical records exceeding 30% and those diagnosed with secondary pancreatic cancer were excluded from the study.

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The event in this study was pancreatic cancer cases who died from pancreatic cancer, and their survival time was defined as the duration in months from the date of diagnosis to the date of death. For censored cases and individuals lacking information on the date of expiry, survival time was calculated from the date of diagnosis to the last-recorded follow-up date. All relevant and eligible data were collected utilizing a constructed proforma. Treatment modalities included surgical resection followed by adjuvant therapy, palliative care and end-of-life care. Anticipating a potential 10% rate of missing values, the study aimed for a total sample size of 335 patients. Details regarding its sample size calculation and the proforma except blood test results have been previously published elsewhere.[8]

The statistical analysis was performed using statistical software for data science (STATA) version 17.0.[9] The data was evaluated using descriptive statistics and Cox regression analysis. Quantitative variables were summarized with mean and standard deviation (SD), while qualitative variables were presented as counts and percentages. For the univariable analysis step of survival analysis, simple Cox regression was utilized to identify potential prognostic factors. Covariates with a significance level (p-value) of 0.25 or lower were selected for inclusion in subsequent multivariable modelling.

Multiple Cox proportional hazards regression was then employed to determine the prognostic factors of the malignancy. $p<0.05$ was considered statistically significant. The parsimonious model, incorporating the fewest significant variables, resulting from the forward stepwise selection method, was chosen in this study. Next, the linearity of continuous variables was assessed using the multivariable fractional polynomials approach via the Fracpoly command. Multicollinearity was then evaluated through a comprehensive examination of the correlation matrix, variance inflation factor (VIF) and tolerance tests. Subsequently, potential two-way biologically or clinically meaningful interaction terms between significant independent variables were evaluated.

After that, the model's specification error was examined using the link test, while the proportional hazard assumptions were evaluated both graphically and through mathematical approach such as the scaled and unscaled Schoenfeld tests and C-statistics. As for model adequacy assessment, regression diagnostic statistics such as checking Martingale residuals, Cox-Snell residuals, deviance residuals and influence analysis were performed. Remedial measures were applied for the influential observations detected from the regression diagnostics. Any observations having regression coefficient changes of more than 20% were deleted from the model.

Final results were presented with both crude and adjusted hazard ratios, accompanied by 95% confidence intervals (95% CI), and their corresponding p-values. The study protocol and ethical aspects were approved by Universiti Sultan Zainal Abidin Human Research Ethics (UHREC) (Study protocol code: UniSZA/UHREC/2020/169) and the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-20-1339-52843 (IRR)).

RESULTS

Between 2011 and 2018, the medical records of total 376 pancreatic cancer patients could be retrieved. Detailed information on these patients, including their baseline characteristics, lifestyle, family cancer history, comorbidities, signs and symptoms at diagnosis, pathological findings, and treatment methods, has been reported previously elsewhere.8 Among the haematological variables, haemoglobin values could be retrieved for only 359 patients. The mean haemoglobin level among pancreatic cancer patients was found to be 12.86 g/dL (SD=1.23). Due to missing values exceeding 30% for other laboratory parameters, those variables were excluded from the analysis.

The potential significant survival predictors of pancreatic cancer were identified by means of simple Cox proportional regression analysis. Considering no other confounding variables, the results of univariable analysis revealed several factors associated with increased risk of mortality among pancreatic cancer patients. These factors included age 60 years and above, female patients (HR: 0.78; 95%CI: 0.57, 1.06), Chinese ethnicity (HR: 1.40; 95%CI: 1.02, 1.91), being married, being widowed or divorced, having history of smoking, alcohol consumption, having family history of pancreatic cancer (HR: 1.39; 95%CI: 0.89, 2.18), comorbidities such as pancreatitis, type II diabetes, hepatitis C (HR: 2.17; 95%CI: 1.01, 4.64), cirrhosis, hypertension (HR: 1.36; 95%CI: 0.99, 1.87), and ischemic heart disease.

Additionally, symptoms at presentation such as abdominal pain, back pain, loss of appetite, fatigue, nausea and vomiting, jaundice (HR: 8.27; 95%CI: 5.67, 12.06), lack of colour in faeces (HR: 7.07; 95%CI: 4.31, 11.60), dark colour urine, fever, abdominal distension, dyspepsia, presence of mass in abdomen (HR: 4.35; 95%CI: 2.72, 6.94) along with haemoglobin levels (HR: 0.40; 95%CI: 0.34, 0.47) were found to significantly impact survival. Furthermore, diagnosed with neuroendocrine tumours, location of tumour at body, receiving palliative treatment (HR: 1.92; 95%CI: 1.25, 2.95) or best supportive care (HR: 14.82; 95%CI: 9.12, 24.10), hepatomegaly and ascites (HR: 6.74; 95%CI: 4.10, 11.09) demonstrated potential effect on survival of the patients.

In the final model after removing two influential observations, several variables were found to be significant prognostic factors for the pancreatic cancer patients' survival. These variables included being female (HR: 0.11; 95%CI: 0.06, 0.17), being of Chinese ethnicity (HR: 1.46; 95%CI: 1.04, 2.06), having a family history of pancreatic cancer (HR: 1.86; 95%CI: 1.13, 3.04), having hepatitis C (HR: 3.90; 95%CI: 1.69, 9.00), having hypertension (HR: 0.61; 95%CI: 0.42, 0.88), presenting with jaundice (HR 8.60; 95%CI: 4.95, 14.94), experiencing a lack of colour in faeces (HR: 3.15; 95%CI: 1.49, 6.64), having a palpable mass in the abdomen (HR: 2.35; 95%CI: 1.34, 4.13), the presence of ascites (HR: 2.52; 95%CI: 1.31, 4.86), haemoglobin (HR: 0.22; 95%CI: 0.16, 0.29), receiving palliative care (HR: 2.28; 95%CI: 1.39, 3.73), and end-of-life/ supportive care (HR: 6.47; 95%CI: 3.54, 11.85). All identified factors were associated with increased risk of mortality while being female, having hypertension, and higher haemoglobin values were linked with decreased mortality risk among pancreatic cancer patients. Table I presents the results of significant variables in univariable and

Table I: Prognostic factors on survival of pancreatic cancers after removing influential observations (n =357)

Variables	Simple Cox Proportional Hazard Regression		Multiple Cox Proportional Hazard Regression	
	Crude Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
Age group				
≤60 years old	1.00			
>60 years old	1.88 (1.37, 2.57)	<0.001		
Sex				
Male	1.00		1.00	
Female	0.78 (0.57, 1.06)	0.108	0.11 (0.06, 0.17)	<0.001
Ethnicity				
Malay	1.00		1.00	
Chinese	1.40 (1.02, 1.91)	0.037	1.46 (1.04, 2.06)	0.031
Indian	1.09 (0.63, 1.89)	0.747	0.84 (0.46, 1.56)	0.587
Marital status				
Single	1.00			
Married	2.01 (0.82, 4.94)	0.127		
Widow/Divorced	2.67 (1.05, 6.77)	0.038		
Smoking				
No	1.00			
Yes	1.48 (1.08, 2.02)	0.014		
Alcohol drinking				
No	1.00			
Yes	2.21 (1.18, 4.12)	0.013		
Family history of CA pancreas				
No	1.00		1.00	
Yes	1.39 (0.89, 2.18)	0.153	1.86 (1.13, 3.04)	0.014
Having pancreatitis				
No	1.00			
Yes	1.80 (0.91, 3.58)	0.093		
Having type II diabetes				
No	1.00			
Yes	1.79 (1.32, 2.42)	<0.001		
Having Hepatitis C				
No	1.00		1.00	
Yes	2.17 (1.01, 4.64)	0.047	3.90 (1.69, 9.00)	0.001
Having cirrhosis				
No	1.00			
Yes	5.29 (1.28, 21.86)	0.021		
Hypertension				
No	1.00		1.00	
Yes	1.36 (0.99, 1.87)	0.054	0.61 (0.42, 0.88)	0.009
Ischaemic Heart Disease				
No	1.00			
Yes	1.84 (1.06, 3.21)	0.031		
Abdominal pain				
No	1.00			
Yes	1.59 (1.18, 2.14)	0.002		
Back pain				
No	1.00			
Yes	1.76 (1.20, 2.58)	0.004		
Loss of appetite				
No	1.00			
Yes	2.17 (1.61, 2.93)	<0.001		
Fatigue				
No	1.00			
Yes	1.65 (1.20, 2.26)	0.002		
Nausea and vomiting				
No	1.00			
Yes	1.35 (0.99, 1.82)	0.056		
Jaundice				
No	1.00		1.00	
Yes	8.27 (5.67, 12.06)	<0.001	8.60 (4.95, 14.94)	<0.001
Lack of colour in faeces				
No	1.00		1.00	
Yes	7.07 (4.31, 11.60)	<0.001	3.15 (1.49, 6.64)	0.003

Table I: Prognostic factors on survival of pancreatic cancers after removing influential observations (n =357)

Variables	Simple Cox Proportional Hazard Regression		Multiple Cox Proportional Hazard Regression	
	Crude Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
Dark colour urine				
No	1.00			
Yes	5.67 (3.09, 10.43)	<0.001		
Fever				
No	1.00			
Yes	3.75 (2.57, 5.49)	<0.001		
Abdominal distension				
No	1.00			
Yes	2.12 (1.40, 3.19)	<0.001		
Dyspepsia				
No	1.00			
Yes	2.12 (1.46, 3.10)	<0.001		
Mass in abdomen				
No	1.00		1.00	
Yes	4.35 (2.72, 6.94)	<0.001	2.35 (1.34, 4.13)	0.003
Having hepatomegaly				
No	1.00			
Yes	2.40 (1.67, 3.44)	<0.001		
Having ascites				
No	1.00		1.00	
Yes	6.74 (4.10, 11.09)	<0.001	2.52 (1.31, 4.86)	0.006
Haemoglobin	0.40 (0.34, 0.47)	<0.001	0.22 (0.16, 0.29)	<0.001
Type of carcinoma				
Exocrine tumour	1.00			
Neuroendocrine tumour	0.39 (0.19, 0.80)	0.010		
Location of tumour				
Head	1.00			
Body	1.34 (0.84, 2.13)	0.221		
Tail	0.80 (0.47, 1.34)	0.395		
Treatment modality				
Surgery& adjuvant therapy	1.00		1.00	
Palliative care	1.92 (1.25, 2.95)	0.003	2.28 (1.39, 3.73)	0.001
End-of-life care	14.82 (9.12, 24.10)	<0.001	6.47 (3.54, 11.85)	<0.001

HR: Hazard ratio; CI: Confidence interval; Forward stepwise variable selection method was applied. Checking the linearity of the continuous variable, multicollinearity and two-way interaction terms, and no problem was identified. The preliminary final model was properly specified (_hat: P<0.037) (_hatsq: P=0.679). The Cox model assumptions were checked graphically by employing various diagnostic plots including the Hazard function plot, Log-minus-log plot, and Schoenfeld partial residuals plot. Additionally, the proportional hazard assumption was assessed for each individual variable in the preliminary final model using both the scaled Schoenfeld test (Separate test) and the unscaled Schoenfeld residual test (Global test) and the assumption was not violated. Regression diagnostics were performed by Martingale residuals, Cox-snell residuals, Deviance residuals and influential analysis. Remedial measures were applied, and two influential observations were omitted from the model.

multivariable analyses in terms of crude and adjusted hazard ratios (HR), their respective 95% CI values, and p-value.

DISCUSSION

Pancreatic cancer is a rapidly lethal malignant neoplasm with poor prognosis, characterized by the mortality to incidence ratio as high as 98%.[10] Given the severity of this disease, there is an urgent need for ongoing research efforts aimed at alleviating suffering and improving survival rates. With regards to this issue, the present study focused on 376 pancreatic cancer patients treated at State Hospitals in Malaysia, examined the multifaceted nature of its prognosis.

Globally, pancreatic cancer exhibits a slight male predominance in both the occurrence of new cases and mortality rates.[4] Consistent with these trends and previous local studies in Malaysia,[11-12] our study documented that nearly 60% of diagnosed cases were male, and female patients had 89% decreased risk of mortality compared to men. The effect of gender on survival outcomes is conflicting; some studies reported poorer survival outcomes among males,[13] while others found no significant gender impact.[14] The influence of gender on cancer survival is likely multifaceted, encompassing factors such as sex differences in molecular or genetic predisposition,[14] and variations in risk exposure, sex hormones, treatment allocation and treatment responses.[15] Furthermore, research exploring these aspects could provide deeper insights into how these factors influencing on gender disparity on pancreatic cancer survival.

Concerning ethnicity, Chinese individuals have historically shown higher rates of pancreatic cancer compared to other ethnicities in Malaysia.[16] However, in the present study, Malays constituted the majority of diagnosed patients, with

Chinese patients representing only 33.2% of the total patient population. This observed ethnic distribution discrepancy may stem from the fact that the majority of data for this study were obtained from State Hospitals which typically serve regions with a higher Malay resident population. In terms of survival outcomes, this study documented a higher mortality risk among Chinese patients compared to Malay cases. Racial disparities in pancreatic cancer incidence and survival may result from modifiable factors such as lifestyle, diet, and physical activity.[17] Genetic and molecular differences unique to each ethnic group could also affect the survival outcomes.[18] Furthermore, variations in cancer awareness and accessibility to healthcare among ethnic groups may contribute to these disparities.[19] However, this study lacked detailed data on these factors, highlighting the need for further research to identify the underlying mechanisms driving these disparities.

There is increasing evidence suggesting an association between a family history of pancreatic cancer and an elevated risk for non-affected family members to develop the disease.[20] In this study, 9.8% of the patients reported the family history, and they exhibited an 86% higher risk of mortality compared to those without such history. These findings are consistent with prior research by Ji et al. in 2008,[21] which also highlighted poorer survival in familial pancreatic cancer cases compared to sporadic cases. Conversely, a study by Omer, Boucher, and DiSario in 2004[22] observed that individuals with a family history of the disease exhibited longer survival, even after accounting for birth year and age at diagnosis. The existing literature on the impact of family history on the survival of pancreatic cancer cases remains limited and inconclusive. Nevertheless, it remains imperative to identify and conduct pancreatic cancer screening among familial high-risk individuals for early detection and timely treatment to promote longer survival.

Hepatitis B and hepatitis C viral infections are primarily linked to liver diseases. However, recent evidence suggests their potential association with extrahepatic malignancies, such as pancreatic cancer. A meta-analysis of observational studies done by Xu et al. in 2013[23] and a meta-analysis of cohort studies by Zhao et al. in 2023[24] provided compelling evidence that an increased risk of pancreatic cancer development with chronic infection of these viruses. In this current study, 2.9% and 2.1% of the total patients had hepatitis B and hepatitis C infection, respectively. Moreover, the study findings suggested that hepatitis C infection, rather than hepatitis B, was associated with a higher risk of mortality. Despite hepatitis B being more infectious than hepatitis C,[25] the latter lacks a vaccine and is more prone to becoming a chronic condition.[26] Their interplay with pancreatic cancer prognosis remains unclear, and understanding their relationship could offer valuable insights into the management and treatment of this malignancy.

Among patients with pancreatic cancer, hypertension is a frequently observed comorbidity, as evidenced by a retrospective study conducted in Poland revealing that 52.6% of such patients presented with hypertension.[27] In this study, 31.1% of the total patients were either on anti-hypertensive medication or had documented hypertension in their medical records. Given its prevalence and potential impact of co-incidence of cancer survival, their association is an area of growing interest, and has inspired its own field of onco-hypertension.[28] Owing to a paucity of data, the literature on their association with survival outcomes remains inconclusive. Interestingly, in our study, hypertension was found to be inversely related with pancreatic cancer mortality which is consistent with findings of 25-year mortality surveillance study.[29] A recent large population-based study in 2022 further demonstrated that pancreatic cancer patients with hypertension who were treated with angiotensin II receptor blockers (ARBs) or angiotensin I-converting enzyme (ACE) inhibitors experienced significantly longer survival. These medications are believed to exert protective effects by modulating pathways involved in tumour growth and metastasis.[30] It is plausible that the hypertensive patients in our study were more likely to be on these medications, which may have contributed to the observed inverse association between hypertension and mortality. However, our study lacked specific data on antihypertensive therapy, limiting our ability to confirm this hypothesis. This underscores the critical need for future research to explore the role of antihypertensive medications in pancreatic cancer survival.

Anaemia is a common occurrence in cancer patients. It affects around half of those undergoing systemic treatment and one-third prior to therapy initiation,[31] with pancreatic ductal adenocarcinoma (PDAC) patients being particularly susceptible.[32] The current study underscores the significance of haemoglobin levels as a crucial prognostic marker for pancreatic cancer patient survival, with lower values indicating an elevated risk of mortality. The literature suggested that nutritional deficiencies and systemic inflammation may impede haemoglobin synthesis, particularly in patients with advanced disease stage.[33] Furthermore, compelling evidence indicates that low haemoglobin levels are associated with poor response to treatment, especially in those with late-stage disease.[34] As a result, those with low haemoglobin values may face higher mortality risk.

In its early stages, pancreatic cancer is clinically asymptomatic. By the time symptoms become apparent, the disease has locally advanced or spread to nearby organs, most commonly to the liver.[35] The clinical presentations documented in this study were nearly comparable to the other studies.[12] Additionally, a considerable portion of patients exhibited clinical indicators suggestive of liver or peritoneal cavity metastasis, including jaundice, pale-coloured stools, abdominal mass, and ascites. The presence of these manifestations indicates advanced-stage disease, and those with such complications may receive less aggressive treatment[36] and might have negative impact on a patient's quality of life.[37] Consequently, in this study, individual presenting signs and symptoms of metastasis were found to have worse prognosis compared to those without such manifestations.

Pancreatic cancer remains a challenging malignancy with limited treatment options, among which surgical resection remains the primary curative approach. Consistent with existing literature, our study demonstrated that patients

undergoing surgical resection with curative intent had the longest survival, whereas those receiving palliative therapy or best supportive care had the poorest outcomes. This aligns with the clinical expectation that patients referred for palliative or supportive care are typically those with advanced, inoperable disease and poor prognoses. These findings underscore the critical importance of early diagnosis and timely surgical intervention. Previous reports have similarly emphasized that surgical resection offers the only chance for cure, although only 15%–20% of cases are diagnosed at a stage where surgery is feasible.[38] However, our study lacked detailed data on the specifics of surgical procedures and the types of chemotherapy or radiotherapy administered, limiting the scope of further analysis. Future research should address these gaps to provide a more comprehensive understanding of treatment approaches and their effects on survival outcomes.

CONCLUSIONS

This retrospective review over an 8-year period provides valuable insights into the prognostic factors influencing the survival of patients with pancreatic cancer, particularly within the Malaysian context. By identifying specific clinical and demographic variables—such as ethnicity, familial history, co-infections, and comorbidities—this research underscores the complexity and multifaceted nature of pancreatic cancer prognosis. The significant association of factors like hepatitis C co-infection, jaundice, and end-of-life care with poorer survival outcomes emphasizes the need for targeted clinical interventions and tailored patient management strategies. Conversely, the identification of protective factors, such as female gender, hypertension, and higher haemoglobin levels, offers new perspectives that could guide future therapeutic approaches. Understanding these prognostic indicators can aid health personnels in more accurately assessing patient risk profiles, thereby facilitating earlier and more personalized interventions. Future research should build on these findings, exploring how these and other factors can be integrated into comprehensive care plans that address the specific needs of diverse patient populations.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Proportions and determinants of successful tuberculosis treatment among tuberculosis patients with comorbidity registered in National Tuberculosis Registry in Negeri Sembilan from year 2018-2023

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ABSTRACT

Introduction: Tuberculosis (TB) is one of the major global health challenges and concerns. Despite the availability of effective treatment in Malaysia, it remained a consistently high notification rate of TB cases. The objective of this study was to determine the proportion of successful TB treatment outcomes and its determinants among TB with comorbidities patients in Negeri Sembilan, Malaysia.

Methods: This is a retrospective cohort study among TB with Comorbidities cases in Negeri Sembilan using multiple secondary surveillance databases: National Tuberculosis Registry (NTBR), National Aids Registry (NAR) and National Diabetic Registry (NDR). The data review was from April 2024 until June 2024. All registered TB cases with comorbidities in Negeri Sembilan from the year 2018 to 2023 were analysed to determine the determinants of successful TB treatment among TB with comorbidities patients.

Results: Out of 712 TB cases with comorbidities, 541 (76.0%) achieved a successful TB treatment outcome, and 171 (24.0%) did not. The successful TB treatment among TB with comorbidities showed predominantly among male (72.5%), Malay ethnicity (65.4%), secondary education level (60.3%), and unemployed working status (70.1%). Diabetes mellitus (DM) was the most common comorbidity (70.4%), followed by hypertension (44.8%), dyslipidaemia (36.0%), HIV (19.5%), and viral hepatitis (18.1%). Factors significantly associated with successful TB treatment were those who had a secondary education level (AOR: 2.222; 95% CI: 1.129, 4.374) and a tertiary education level (AOR: 4.474; 95% CI: 1.428-14.01), were diagnosed with TB in the government hospital (AOR: 0.053; 95% CI: 0.008-0.376), and were not done Acid-Fast Bacillus sputum in the intensive phase of treatment (AOR: 0.191; 95% CI: 0.046, 0.785), cases followed the Directly Observed Therapy at the intensive phase (AOR: 9.045; 95% CI: 4.604, 17.770), and the treatment duration was more than 6 months (AOR: 6.511; 95% CI: 3.383, 12.532).

Conclusion: The successful treatment outcome for TB with comorbidities still falls short of the target and, if not treated well, could potentially lead to prolonged disease transmission, higher mortality rates, and increased healthcare costs. Identifying the proportion of successful treatment rates and their determinants provides insight into the disease burden and helps the public health sector and medical professionals assess and take appropriate action to improve local integration and collaborative service approaches for TB patients with concurrent comorbidities.

KEYWORDS:
Tuberculosis, comorbidity, registry, Directly Observed therapy, treatment outcome

INTRODUCTION

Tuberculosis (TB) is a global health challenge and concern, with alarming rates of incidents in various parts of the world. The latest global report has revealed that in 2022, 7.5 million persons were newly diagnosed with TB, making it the world's second leading cause of death from a single infectious agent after COVID-19.[1] Patients who had both comorbidities and health-related risk factors, such as diabetes, human immunodeficiency virus (HIV), alcohol use disorders, tobacco smoking, mental disorders, malnutrition, and viral hepatitis, accounted for 4.5 million (45%) of the reported new and relapsed TB cases.[2] However, the COVID-19 pandemic has temporarily altered the pattern of TB incidence worldwide and masked the true extent of the disease.[3] The pandemic-induced disruptions in healthcare institutions have resulted in a lack of reporting, distorting data, and impeding an appropriate evaluation of the incidence of TB.[4]

Malaysia, an intermediate burden country with TB, remained a consistently high incidence notification case despite the availability of effective treatment that can complete recovery when diagnosed and treated properly. According to data from the Malaysia Ministry of Health (MOH), there was an increase in the incidence of TB cases by 17% from 2021 to 2022.[5] Negeri Sembilan is one of the states in Malaysia, having an estimated 1.2 million population that showed the highest annual increase with a 5.1% annual increase (ARR: 5.1%) from the year 2012 to 2016.[6,7]

Patients who are incomplete in their treatment for TB will impose a substantial financial burden on the government.

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The average cost per patient in this group is RM901.63 (215.49 USD), which is four times more than the cost of therapy for patients who have completed their treatment.[8] The cost of treating patient TB with comorbidities and hospital stays was 4.5 times higher than that of treating TB without comorbidities.[8]

One of the significant challenges in the current effort to control TB spread would be managing TB patients with comorbidities, in which the comorbidities worsen the effects of TB, particularly resulting in a lower success rate in treatment and a higher incidence of death. Evaluating the treatment success rate outcome is a crucial measure in the End TB Strategy 2035. It is recommended that a tuberculosis program must achieve a treatment success rate of at least 90% and a cure rate of 85% to operate effectively.[9,10]

Nevertheless, Malaysia recently reported a successful treatment rate of 79% in 2021 among TB patients who received treatment at the national level, which is far from the target.[9] Besides that, data regarding the proportion of successful treatment rates among TB patients with comorbidities is scarce in Malaysia compared to the general population. This disparity highlights a critical gap in the healthcare system's ability to address the unique challenges faced by these specific populations effectively. The treatment success gap between the general TB population and those with comorbidities results in prolonged disease transmission, higher mortality rates, and increased healthcare costs.[11]

To achieve this goal, it is important to address health-related risk factors and comorbidities such as Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), diabetes mellitus (DM), viral hepatitis, depression, and malnutrition as components of pillar 1 of the End TB Strategy, which focuses on integrated patient-centred care and prevention, including action on TB and comorbidities.[12] This study aims to determine the proportion of successful TB treatment outcomes and its determinants among TB patients with comorbidities in Negeri Sembilan from 2018-2023.

MATERIALS AND METHODS

A retrospective cohort study involving TB patients with comorbidities in Negeri Sembilan was conducted by utilising the secondary data obtained from the Malaysian National Tuberculosis Registry (NTBR) and only TB data that was registered under the Negeri Sembilan State Health Office (Jabatan Kesihatan Negeri, Negeri Sembilan, JKNNS) surveillance registry was selected for the present study.

The NTBR is a web-based system managed by the Ministry of Health Malaysia. Its purpose is to continuously collect data and manage actions pertaining to the notification, registration, investigation, and treatment of TB cases across all states in Malaysia. The Prevention and Control of Infectious Diseases Act 1988 (Act 342) mandates the notification of all TB cases to the district health office.[13]

The NTBR in JKNNS consisted of data from seven district health offices (Seremban, Port Dickson, Kuala Pilah, Rembau, Tampin, Jempol, and Jelebu) that were responsible for monitoring the surveillance system of TB cases registered at all the health facilities in Negeri Sembilan. The sampling frame for this study consisted of all TB registered under NTBR and follow-up in health facilities in the year 2018-2023 in Negeri Sembilan.

The study included TB patients with comorbidities who met the inclusion criteria; patients who did not match these criteria were excluded. The inclusion criteria were: (i) newly diagnosed TB-comorbidities cases from 1st January 2018 until 31st December 2022; (ii) TB-comorbidities cases notified through the NTBR from January 2018 until December 2022; and (iii) TB-comorbidities aged > 18 years old. Exclusion criteria included (i) incomplete data on the independent variable, (ii) the case with incomplete data on treatment outcome (transferred to another state or defaulter), and (ii) multidrug-resistant tuberculosis.

The sample size for this study was determined using OpenEpi software version 3.01 using a single proportion formula with a 95% confidence interval (CI) and 5% absolute precision, applying an 81.49% proportion of TB treatment success among the TB-DM based on the largest sample size from a previous study performed in Malaysia.[14] The minimum sample required in this study was 279, including a 20% attrition rate. Given that the present study utilised secondary data, all cases fulfilling the inclusion criteria would be included in the analysis.

TB and HIV are mandatory notifiable diseases by law under Act 342.[13] Each respective district needs to register all TB cases that have been notified into the NTBR system. The definition stated in Malaysia's case definition of infectious disease confirmed both cases.[15] All confirmed DM patients must register at National Diabetes Registry (NDR) for surveillance and monitoring.[16]

This study used three national databases. The main data and variables were extracted from the NTBR under health facilities in Negeri Sembilan. The National AIDS Registry (NAR) and the NDR were cross-referenced as additional information to ensure comprehensive comorbidities data. The data owner performed the confirmatory process using the deterministic matching method, where three national databases were used to connect by using the unique identification number.

Twenty-three variables were extracted from the NTBR for the present analysis. The outcome variables for this study were coded as successful (yes/no). Successful TB treatment outcomes included TB patients who are (i) cured (bacteriologically confirmed TB patient who subsequently smear/culture negative during the last month of the treatment or on at least one previous occasion and was input in NTBR as 'cured'.) and ii) completed treatment (patient who completed TB treatment without meeting the criteria for cure or treatment failure was input in NTBR as 'completed treatment'.)[17]

People who finished TB treatment but did not meet the criteria for cure or treatment failure were also entered into NTBR. Unsuccessful TB treatment included (i) treatment failure (TB patient whose sputum smear or culture was

positive at 5 months or later during treatment and was input in NTBR as 'treatment failure'.), (ii) death (passes away for any reason before or during TB treatment all-cause mortality and was input in NTBR as 'died') or (iii) loss of follow-up (patient who did not initiate treatment or whose treatment was interrupted for two consecutive months or more and entered into NTBR as 'loss to follow up'). The twenty-three independent variables were categorised into three main domains. Seven variables were sociodemographic factors, twelve variables related to the TB disease profile and four variables related to the TB treatment profile.

Data Management and Analysis

Figure 1 depicted the data retrieval and extraction process which incorporated three national data sources in the form of Microsoft Excel Open XML Spreadsheet (xlsx) format. Data received from JKN Negeri Sembilan was 754. Data from NAR (n= 737) and NDR (n=126,689) had been confirmed for comorbidities with the NTBR data. The data owner performed this data linkage using the deterministic matching method, where three national databases were linked by using the unique identification number. Data cleaning was performed using the final database (n = 754). Of 754 total samples, 712 (94.4%) were found eligible for analysis after applying the inclusion and exclusion criteria. The final database (n = 712) was imported into IBM SPSS version 29.0 for further statistical analysis. The analysis used in this study included descriptive and inferential analysis. The TB treatment success rate (proportion of subjects having successful TB treatment in the present study) was calculated by using the formula as follows:

$$\text{Rate of successful TB treatment} = \frac{\text{Number of successful TB treatment among TB patient with comorbidity}}{\text{Total number of newly diagnosed TB patient with comorbidity in year 2018-2023}}$$

Estimation of the rate of successful TB treatment (95% confidence interval for the proportion interval) was calculated using the formula below:

$$95\%\ \text{Confident interval (CI)} = p \pm z^* \frac{p\,(1-p)}{n}$$

Descriptive analysis was performed to describe the characteristics of participants (sociodemographic), TB disease profile and TB treatment profile determinants. The mean (standard deviation, SD) was presented for the continuous variable. The frequency (n) and percentage (%) were presented for the categorical variables. The distribution of TB with comorbidities was presented in general and based on their treatment outcomes. The distribution was compared using descriptive and univariable analysis, such as the chi-square test for homogeneity. independent t-test and the continuity correction test.

Logistic regression analyses were performed to estimate the crude and adjusted effect of the independent variables of successful TB with comorbidities treatment. The variables were included in the multiple logistic regression model based on the statistical significance of a p-value (< 0.25). The backward LR method was used to select the variables. Subsequently, the initial model was evaluated for, interaction, linearity in the logit and multicollinearity. The Hosmer-Lemeshow goodness-of-fit test, classification table, and receiving operating characteristic (ROC) curve were used to confirm the model's fitness. The crude/adjusted odds ratio (OR), 95% CI, and their respective p-values were used to demonstrate the strength of association between all variables and the outcome measure. The statistical test was performed with a significance level of 0.05.

Ethics Approval

Two institutional review boards approved this study, which adhered to the standards outlined in the Declaration of Helsinki. The study gained ethical clearance from two institutions in May 2021: i) the Research Ethics Committee (REC) at UiTM (100 - FPR (PT.9/19) (FERC-EX-24-02)), and ii) the Medical Research Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR ID-24-00551-JKK (IIR)). The data owner secured the anonymity of participants by deleting all identifying information from the database, thereby maintaining confidentiality in this study. All data was submitted to a password-protected computer belonging to a researcher. Researchers were the sole recipients of the data. The research findings did not reveal any personal information, and the participants could not be identified.

RESULTS

A total of 712 TB patients with comorbidities were recruited, with 541 (76.0%) achieving a successful TB treatment outcome and 171 (24.0%) experiencing an unsuccessful TB treatment outcome. Table I shows the trend rate of successful TB treatment among TB patients with comorbidities, which ranged from 70.3% (62.7%–77.9%) to 79.9% (73.2%–86.6%) from 2018 to 2022. Table II shows the characteristics of TB with comorbidities, which are predominantly male (74.0%), the mean age 53 (14) years old, and Malay ethnicity (66.3%). The successful TB treatment among TB with comorbidities was predominantly found among Malaysian males aged 40 to 59 years old (50.5%), Malay ethnicity (65.4%), residing urban area (60.3%), secondary education level (60.3%), and unemployed working status (70.1%).

DM was the most common comorbidity (70.4%), followed by hypertension (44.8%), dyslipidaemia (36.0%), HIV (19.5%), and viral hepatitis (18.1%). Patients with TB and DM showed a high percentage of successful TB treatment (76.0%) compared to other comorbidities, ranging between 13.5% and 48.6%. Regarding the characteristics of the TB treatment profile, a high percentage of successful TB treatment was found in patients who were Acid-Fast Bacillus (AFB) converted in the intensive phase (84.5%) and patients who followed Directly Observed Therapy (DOT) during the intensive phase (95.0%).

Simple logistic regression analysis demonstrated that fourteen variables (i.e., education level, occupation, citizenship, TB anatomy location, sputum AFB (diagnosis), CXR upon diagnosis, health facility: TB diagnosis, AFB sputum in the intensive phase, DOTs (intensive), health facility: initiated TB treatment, treatment duration, age, gender, and ethnicity) were significantly associated with successful TB treatment at the level of significance set at p = 0.25 (Table III).

Table I: The rate of successful TB treatment trend among TB with comorbidities from 2018-2023 in Negeri Sembilan

	Rate successful treatment among TB with comorbidities from 2018-2022				
	2018	**2019**	**2020**	**2021**	**2022**
Total TB patients with comorbidities cases registered	122	179	139	134	138
Successful treatment Outcome	95	134	111	104	97
Rate of Successful Treatment (%) (95%CI)	77.9% (70.5%-85.3%)	74.9% (68.5%-81.3%)	79.9% (73.2% - 86.6%)	77.6% (70.5%-84.7%)	70.3% (62.7%-77.9%)
Cured	75	107	77	85	67
Completed treatment	20	27	34	19	30
Unsuccessful Treatment Outcome	27	45	28	30	41
Loss to follow-up	5	7	4	5	1
Treatment Failed	0	2	0	1	0
Died	22	36	24	24	40

Table II: Characteristics of TB with comorbidities in total and according to the TB treatment outcomes, 2018-2023 (n= 712)

Variables	**Total (n = 712) Mean (SD)/n (%)**	**Successful TB Treatment (n = 541) Mean (SD)/n (%)**	**Unsuccessful TB Treatment (n = 171) Mean (SD)/n (%)**	***p-value**
Socio-demographic				
Age	53 (14)	53 (13)	54 (16)	0.457[a]
18 to 39 year old	131 (18.4)	96 (17.7)	35 (20.5)	0.320[c]
40 to 59 year old	348 (48.9)	273 (50.5)	75 (43.8)	
≥ 60 year old	233 (32.7)	172 (31.8)	61 (35.7)	
Gender				
Male	527 (74.0)	392 (72.5)	135 (78.9)	0.092[c]
Female	185 (26.0)	149 (27.5)	36 (21.1)	
Ethnicity				
Malay	472 (66.3)	354 (65.4)	118 (69.0)	0.119[c]
Chinese	95 (13.3)	72 (13.3)	23 (13.5)	
Indian	114 (16.0)	95 (17.6)	19 (11.1)	
Others	31 (4.4)	20 (3.7)	11 (6.4)	
Location of residence				
Rural	287 (40.3)	215 (39.7)	72 (42.1)	0.583[c]
Urban	425 (59.7)	326 (60.3)	99 (57.9)	
Education level				
No Formal Education	120 (16.9)	74 (13.7)	46 (26.9)	< 0.001[c]
Primary Education	95 (13.3)	73 (13.5)	22 (12.9)	
Secondary Education	413 (58.0)	326 (60.3)	87 (50.9)	
Tertiary Education	84 (11.8)	68 (12.5)	16 (9.3)	
Occupation				
Unemployed	517 (72.6)	379 (70.1)	138 (80.7)	0.007[c]
Employed	195 (27.4)	162 (29.9)	33 (19.3)	
Citizenship				
Malaysian	694 (97.5)	531 (98.2)	163 (95.3)	0.076[b]
Non-Malaysian	18 (2.5)	10 (1.8)	8 (4.7)	
TB-Disease Profile				
Detection Mode				
Active	72 (10.1)	51 (9.4)	21 (12.3)	0.281[c]
Passive	640 (89.9)	490 (90.6)	150 (87.7)	
TB Anatomy Location				
Pulmonary TB	624 (87.6)	488 (90.2)	136 (79.5)	< 0.001[c]
Extrapulmonary TB	88 (12.4)	53 (9.8)	35 (20.5)	
Sputum AFB (diagnosis)				
Positive	518 (72.8)	419 (77.4)	99 (57.9)	< 0.001[c]
Negative	157 (22.1)	101 (18.7)	56 (32.7)	
Not Done	37 (5.2)	21 (3.9)	16 (9.4)	
Smoking				
Smoking	306 (43.0)	237 (43.8)	69 (40.4)	0.426[c]
Non-Smoking	406 (57.0)	304 (56.2)	102 (59.6)	
BCG Scar				
Absent	72 (10.1)	52 (9.6)	20 (11.7)	0.431[c]
Present	640 (89.9)	489 (90.4)	151 (88.3)	

Table II: Characteristics of TB with comorbidities in total and according to the TB treatment outcomes, 2018-2023 (n= 712)

Variables	Total (n = 712) Mean (SD)/n (%)	Successful TB Treatment (n = 541) Mean (SD)/n (%)	Unsuccessful TB Treatment (n = 171) Mean (SD)/n (%)	*p-value
CXR upon diagnosis				
No Lesion	82 (11.5)	61 (11.3)	21 (12.3)	0.154[c]
Minimal	337 (47.3)	258 (47.7)	79 (46.2)	
Moderate	270 (38.0)	209 (38.6)	61 (35.7)	
Advanced	23 (3.2)	13 (2.4)	10 (5.8)	
Health Facility: TB Diagnosis				
Private	28 (3.9)	26 (4.8)	2 (1.2)	< 0.001[c]
Government Clinic	222 (31.2)	212 (39.2)	10 (5.8)	
Government Hospital	462 (64.9)	303 (56.0)	159 (93.0)	
Diabetes Mellitus				
No	211 (29.6)	130 (24.0)	81 (47.4)	< 0.001[c]
Yes	501 (70.4)	411 (76.0)	90 (52.6)	
Hypertension				
No	393 (55.2)	278 (51.4)	115 (67.3)	< 0.001[c]
Yes	319 (44.8)	263 (48.6)	56 (32.7)	
Dyslipidaemia				
No	456 (64.0)	329 (60.8)	127 (74.3)	0.001[c]
Yes	256 (36.0)	212 (39.2)	44 (25.7)	
HIV				
No	573 (80.5)	468 (86.5)	105 (61.4)	< 0.001[c]
Yes	139 (19.5)	73 (13.5)	66 (38.6)	
Viral Hepatitis				
No	583 (81.9)	451 (83.4)	132 (77.2)	0.068[c]
Yes	129 (18.1)	98 (18.1)	39 (22.8)	
TB-Treatment Profile				
AFB Conversion in the Intensive Phase				
No	41 (5.8)	38 (7.0)	3 (1.8)	< 0.001[c]
Yes	503 (70.6)	457 (84.5)	46 (26.9)	
Not Done	168 (23.6)	46 (8.5)	122 (71.3)	
DOTS (intensive)				
No	134 (18.8)	27 (5.0)	107 (62.6)	< 0.001[c]
Yes	578 (81.2)	514 (95.0)	64 (37.4)	
Treatment duration	6 (3.5)	7 (1.3)	2 (1.2)	< 0.001[a]
< 6 Month	453 (63.6)	298 (55.1)	155 (90.6)	< 0.001[c]
> 6 Month	259 (36.4)	243 (44.9)	16 (9.4)	
Health Facility: Initiated TB Treatment				
Private	26 (3.6)	25 (4.6)	1 (0.6)	< 0.001[c]
Government Clinic	222 (31.2)	210 (38.8)	12 (7.0)	
Government Hospital	464 (65.2)	306 (56.6)	158 (92.4)	

Notes: AFB =Acid Fast Bacillus; BCG= Bacillus Calmette–Guérin vaccine; CXR = Chest X-ray; DOT = Directly Observed Therapy; Human Immunodefiency Virus=HIV; SD = standard deviation; [a]Independent t-test/ [b]continuity correction (Yates' correction); [c]Chi-square test for homogeneity.

Subsequently, when adjusted, those who had a secondary education level (AOR: 2.222; 95% CI: 1.129, 4.374) and a tertiary education level (AOR: 4.474; 95% CI: 1.428-14.01), were diagnosed with TB in the government hospital (AOR: 0.053; 95% CI: 0.008-0.376), and were not done AFB sputum in the intensive phase of treatment (AOR: 0.191; 95% CI: 0.046, 0.785), cases followed the DOTs at the intensive phase (AOR: 9.045; 95% CI: 4.604, 17.770), and the treatment duration was more than 6 months (AOR: 6.511; 95% CI: 3.383, 12.532) were associated with successful TB treatment (Table IV).

DISCUSSION

This study is intended to determine the success rate of TB treatment and its determinants among TB patients with comorbidities in Negeri Sembilan in 2018-2023. Our study data demonstrated that TB patients with comorbidities accounted approximately 24.0% of the reported new and relapsed TB cases and had successfully achieved TB treatment outcomes ranging between 70.3% and 79.9%.[18] This finding is significantly lower than the previous study carried out in India and Poland, which documented a success rate of 86.67% and 88% among TB cases with comorbidities.[11,19] The successful treatment rate showed slightly decrease from the year 2020 to 2022. This finding could be possible due to the disruption of TB management and treatment during the COVID-19 pandemic.[20]

Table III: Univariate Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	Crude OR (95% CI)	*P- value
Sociodemographic				
Age				
18 to 39 year old			1	ref.
40 to 59 year old	0.283 (0.237)	1.43 (1)	1.327 (0.835-2.11)	0.232*
>60 year old	0.028 (0.247)	0.012 (1)	1.028 (0.633-1.669)	0.911
Gender				
Male			1	ref.
Female	0.354 (0.211)	2.826 (1)	1.425 (0.943-2.155)	0.093*
Ethnicity				
Malay			1	ref.
Chinese	0.043 (0.262)	0.026 (1)	1.043 (0.624-1.744)	0.871
Indian	0.511 (0.273)	3.505 (1)	1.667 (0.976-2.845)	0.061*
Others	-0.501 (0.39)	1.648 (1)	0.606 (0.282-1.302)	0.199*
Location of residence				
Rural			1	ref.
Urban	0.098 (0.178)	0.302 (1)	1.103 (0.778-1.563)	0.583
Education level				
No Formal Education			1	ref.
Primary Education	0.724 (0.307)	5.552 (1)	2.063 (1.13-3.767)	0.018*
Secondary Education	0.846 (0.223)	14.353 (1)	2.329 (1.504-3.607)	<.001*
Tertiary Education	0.971 (0.335)	8.392 (1)	2.642 (1.369 -5.098)	0.004*
Occupation				
Unemployed			1	ref.
Employed	0.581 (0.215)	7.276 (1)	1.787 (1.172-2.726)	0.007*
Citizenship				
Non-Malaysian			1	ref.
Malaysian	0.958 (0.483)	3.938 (1)	2.606 (1.012-6.713)	0.047*
TB-Disease Profile				
Detection Mode				
Active			1	ref.
Passive	0.296 (0.276)	1.157 (1)	1.345 (0.784-2.308)	0.282
TB Anatomy Location				
Extrapulmonary TB			1	ref.
Pulmonary TB	0.863 (0.238)	13.094 (1)	2.37 (1.485-3.781)	<.001*
Sputum AFB (diagnosis)				
Not Done			1	ref.
Positive	1.171 (0.35)	11.181 (1)	3.225 (1.623-6.405)	<.001*
Negative	0.318 (0.371)	0.733 (1)	1.374 (0.664-2.845)	0.392
Smoking				
Smoking			1	ref.
Non-Smoking	-0.142 (0.178)	0.633 (1)	0.868 (0.612-1.231)	0.426
BCG Scar				
Absent			1	ref.
Present	0.22 (0.279)	0.619 (1)	1.246 (0.721-2.152)	0.431
CXR upon diagnosis				
Advanced			1	ref.
Moderate	0.969 (0.445)	4.741 (1)	2.636 (1.102-6.306)	0.029*
Minimal	0.921 (0.44)	4.386 (1)	2.512 (1.061-5.949)	0.036*
No Lesion	0.804 (0.491)	2.683 (1)	2.234 (0.854-5.848)	0.101*
Health Facility: TB Diagnosis				
Private			1	ref.
Government Clinic	0.489 (0.802)	0.372 (1)	1.631 (0.339-7.853)	0.542
Government Hospital	-1.92 (0.874)	6.727 (1)	0.147 (0.034-0.626)	0.009*
TB Treatment Profile				
AFB Conversion in the Intensive Phase				
No			1	ref.
Yes	-0.243 (0.619)	0.154 (1)	0.784 (0.233-2.64)	0.695*
Not Done	-3.514 (0.624)	31.702 (1)	0.03 (0.009-0.101)	<.001*
DOTS (intensive)				
No			1	ref.
Yes	3.46 (0.253)	187.229 (1)	31.828 (19.388-52.247)	<.001*
Treatment duration				
< 6 Month			1	ref.
> 6 Month	2.067 (0.276)	55.896 (1)	7.9 (4.595-13.58)	<.001*

Table III: Univariate Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	Crude OR (95% CI)	*P- value
Health Facility: Initiated TB Treatment				
Private			1	ref.
Government Clinic	-0.357 (1.062)	0.113 (1)	0.7 (0.087-5.613)	0.737
Government Hospital	-2.558 (1.024)	6.234 (1)	0.077 (0.01-0.577)	0.013*

Notes: B = unstandardised regression weight; CI = Confidence interval; df = degree of freedom; SE = Standard error; OR = odds ratio; BCG= Bacillus Calmette–Guérin vaccine; CXR = Chest X-ray; DOT = Directly Observed Therapy; AFB =Acid Fast Bacillus; *level of significance set at 0.25

Table IV: Multivariable Analysis of Determinant TB Successful Treatment Outcome Among TB with Comorbidity (n= 712)

Variables	B (SE)	Wald (df)	AOR (95% CI)	*P- value
Education level				
No Formal Education			1	ref.
Primary Education	0.916 (0.474)	3.730 (1)	2.499 (0.986-6.333)	0.053
Secondary Education	0.798 (0.346)	5.340(1)	2.222 (1.129-4.374)	0.021
Tertiary Education	1.498 (0.583)	6.614 (1)	4.474 (1.428-14.01)	0.010
Health Facility: TB Diagnosis				
Private			1	ref.
Government Clinic	-0.983 (1.064)	0.855 (1)	0.374 (0.047-3.008)	0.355
Government Hospital	-2.928 (0.999)	8.596 (1)	0.053 (0.008-0.376)	0.003
AFB Conversion in the Intensive Phase				
No			1	ref.
Yes	0.557 (0.689)	0.654 (1)	1.746 (0.453-6.734)	0.419
Not Done	-1.656 (0.721)	5.267 (1)	0.191 (0.046-0.785)	0.022
DOTS (intensive)				
No			1	ref.
Yes	2.202 (0.345)	40.846 (1)	9.045 (4.604-17.770)	<0.001
Treatment duration				
< 6 Month			1	ref.
> 6 Month	1.873 (0.334)	31.445 (1)	6.511 (3.383-12.532)	<0.001

Notes: AOR = adjusted odds ratio; B = unstandardised regression weight; CI = confidence interval; df = degree of freedom; SE = Standard error; *level of significance set at 0.05; Cox & Snell R Square:0.435; Constant = 0.831; Backward LR method was applied; No multicollinearity and no interaction; Hosmer Lemeshow test, P-value = 0.063; Classification table 90.9% correctly classified; Area under Receiver Operating Characteristics (ROC) curve = 0.92

In recent years, the treatment success rates for new tuberculosis cases in Malaysia increased steadily from 76% in 2013 to 81% in 2017 for the group of patients studied. Nevertheless, the rates remained below the target of ≥90%.[21] In Negeri Sembilan in 2021, the success rate among general TB cases was 92%, which met the recommendation target.[18] However, the success treatment rate among TB with comorbidities remains low. Therefore, these findings underscore the significance of tuberculosis in the comorbidities population, emphasizing the need for TB management and treatment to meet the success rate target.

The demographic characteristics observed in this study, such as the higher representation of middle-aged adult groups (40 - 59 years old) and males, were consistent with the prevailing global trends in tuberculosis epidemiology.[22] One study found that males are more likely to have multiple comorbidities than females due to more exposure to risk factors.[23] Furthermore, older age increases the risk associated with multiple comorbidities compared to younger age.[24] In terms of treatment outcome, males and older adults have a lower successful treatment outcome compared to females and younger adults.[25] Thus, these findings suggest a more comprehensive gender-responsive approach to addressing the dual challenge of infectious diseases and non-communicable diseases in an ageing population, particularly among patients with tuberculosis and chronic illnesses.

We also found the predominance of DM as a comorbidity compared to other diseases. A similar finding reported in Poland, where DM was the most common comorbidity (5.9%).[11] The TB treatment outcome among TB patients with DM shows a high success rate compared to other diseases. This finding is in concordance with another local study in Kelantan, which reported a high success rate for treatment among TB and DM.[14] This could shed light on the significant efforts made by the Ministry of Health to provide exceptional care and enhance the dual management of patients with co-morbidities within the existing health system. The latest Clinical Practice Guidelines (CPG) for Managing Tuberculosis recommends that all newly diagnosed with tuberculosis undergo regular screening for DM and HIV.[26]

Furthermore, TB cases with comorbidities having higher education levels were found to have higher odds of achieving successful TB treatment compared to those with low

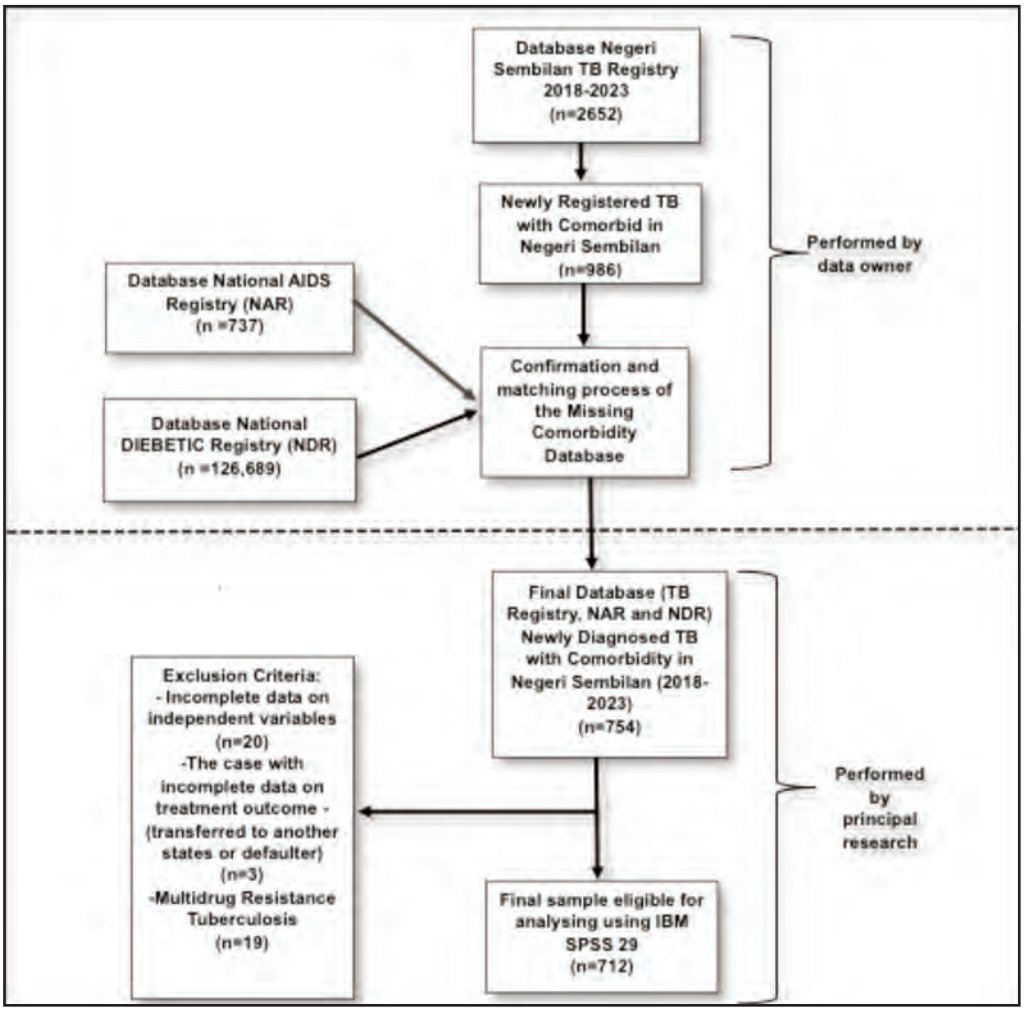

Fig. 1: Flow chart of data retrieval and extraction

education levels. Congruently, a local retrospective cohort study reported lower education levels associated with unsuccessful TB treatment outcomes.[21] These findings could be associated with health literacy and better understanding of treatment regimens. Educated patients are more likely to adhere to medication and follow the instructions, thereby improving treatment outcomes.[27]

This study also found that TB patients with comorbidities diagnosed at government hospitals were found to have lower odds 0.053 (95% CI: 0.008-0.376) of achieving successful treatment outcomes compared to private facilities. According to this finding, corresponding to another study in Lagos, Nigeria,[28] the treatment success rate among private health facilities was 78.09%, which was relatively higher compared to government health facilities. However, studies from Thailand and Vietnam showed that private health facilities were associated with poor TB treatment outcomes.[29-30] This finding may stem from the fact that patients who delay or present late for TB cases typically end up in a government hospital, potentially influencing the treatment outcome. The comorbidity, particularly HIV co-infection, can influence treatment delay.[31] Moreover, government hospitals also normally receive more patients in comparison to private hospitals, which can strain their capacity to provide individualised care.[32] Poor TB outcomes may result from overburdened healthcare systems delivering suboptimal care. Therefore, managing TB with comorbidities requires integration and collaboration between government hospitals, primary health clinics, and private health facilities. It includes strong and effective active case detection for early detection and treatment, given the effectiveness of integrating dual management between TB and DM in increasing successful TB treatment.[33]

Additionally, patients who were consistently on DOTs during the intensive phase were nine times more likely to have TB treatment success than those who were not on DOTs. Other studies strongly support this finding, demonstrating that DOTs can enhance the cure rate.[34] On the other hand, findings from a local study showed that not adhering to DOTs is one of the determinants of unsuccessful TB treatment outcomes among TB and HIV patients.[35] One possible reason is that TB patients with comorbidities perceive a greater risk of complications from tuberculosis, which may increase their motivation to adhere to their treatment regimens rigorously. Better compliance may be stimulated by the perceived severity of their condition.[36-37]

Furthermore, the other significant determinant of successful treatment was the duration of treatment more than six months. This study found that the odds of successful TB treatment were four times higher if the treatment lasted more than six months compared to less than six months. This finding is similar to a cross-sectional study conducted in Kelantan, which also found that the duration of treatment for TB patients with HIV was a significant determinant of successful treatment outcomes.[38] The prolonged therapy regimens ensure that all tuberculosis bacteria are eradicated, as they may be inactive or slow-growing. Shorter courses of antibiotics are less effective in eliminating all microorganisms from the body, increasing the likelihood of a relapse. WHO strongly recommends a six-month treatment period for all drug-susceptible TB patients, with high certainty of evidence.[39]

The retrospective cohort study design facilitates a better understanding of the determinant of successful TB treatment outcome among TB with comorbidities compared to the usual studies that focus on TB with single comorbidity as the study population.[35, 38] To the best of our knowledge, we report the latest original study assessing the determinants of successful treatment of TB with comorbidities in Negeri Sembilan. In addition, this study uses three national registry databases, which minimizes data missingness on comorbidities within the study population. The integration and merging into multi-centre registry will provide more accurate data sources and facilitates better coordination and continuity of care.[40] This study also emphasised the importance of collaborative and integrated activity in managing TB patient with comorbidities to improve the treatment outcomes.

One limitation of this study is that the analysis based on secondary surveillance data is limited by the data's completeness, such as insufficient data on other health-related factors, such as alcohol status, malnutrition and depression status.[2] Although this study demonstrates internal validity, it cannot be generalised to other states due to its single-state setting, however present findings could alert the state authorities for future policy making.

CONCLUSION

The successful treatment outcome for TB with comorbidities still falls short of the target and, if not treated well, could potentially lead to prolonged disease transmission, higher mortality rates, and increased healthcare costs. Identifying the proportion of successful treatment rates and their determinants provides insight into the disease burden. It helps the public health sector and medical professionals assess and take appropriate action to improve local integration and collaborative service approaches for TB patients with concurrent comorbidities.

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CONFLICT OF INTEREST AND FUND

None

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ORIGINAL ARTICLE

Predictors of acupuncture referral for chronic non-specific low back pain among medical practitioners in Malaysia

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ABSTRACT

Introduction: Chronic non-specific low back pain (cnLBP) is a common primary care health issue. While acupuncture offers promising potential as a complementary treatment, its acceptance and integration into standard medical care for cnLBP remains inconsistent. This study investigated the predictors of acupuncture referral for cnLBP using the Theory of Planned Behaviour (TPB).

Materials and Methods: This was a cross-sectional observational study. Medical practitioners were recruited from the Malaysian Medical Association via email invitations. Data were collected via a validated online questionnaire and analysed using SPSS, employing bivariate correlation and multiple linear regression analyses to examine the predictors of referral behaviour.

Results: A total of 389 medical practitioners were recruited. The respondents were predominantly general practitioners aged 35–44 years, with 10–19 years of clinical experience, and approximately 90.0% managed cnLBP. Despite the high awareness of the Traditional and Complementary Medicine Act (92.0%), only 33.2% referred patients to acupuncture. Few had acupuncture training (3.6%) or personal experience (7.7%), and services were available in 12.1% of the workplaces. Medical practitioners possess substantial knowledge about acupuncture treatment for cnLBP; however, misconceptions and uncertainties regarding its mechanisms persist. Using multiple linear regression analysis, the significant predictors of acupuncture referral were self-experience (β=0.151, p<0.01), attitude (β=0.189, p<0.001), and perceived behavioural control (β=0.101, p<0.05).

Conclusions: Despite positive attitudes and substantial awareness, barriers hinder the broader integration of acupuncture in cnLBP treatment. Targeted education, institutional support, and enhanced research collaborations are essential for improving referral rates and expanding the treatment options for cnLBP.

KEYWORDS:
Acupuncture referral, chronic low back pain, planned behaviour

INTRODUCTION

Acupuncture is a longstanding therapeutic practice, having roots in China for over 2,500 years.[1] It has attracted interest within the modern medical community, with studies demonstrating its effectiveness in treating various health conditions.[2,3] In 2020, given the increased demand for acupuncture, the "WHO Benchmark for the Practice of Acupuncture" was published to emphasise critical elements for the safe practice of acupuncture.[4] The National Policy of Traditional and Complementary Medicines (T&CM) proposed the integration of T&CM into the national healthcare system.[5] Therefore, acupuncture is now recognised in Malaysia under the T&CM Act.[6] There are 16 T&CM units in the Ministry of Health (MOH) hospitals offering various modalities, and acupuncture is offered in 14 units. Registered medical practitioners refer patients seeking treatment to T&CM units after definitive diagnoses.[7] Patients are then further screened by T&CM unit healthcare staff to ensure they are suitable for T&CM treatment. Furthermore, to ensure standardisation of care, the MOH has published guidelines on acupuncture use, and the indicated conditions include chronic pain, stroke rehabilitation, and post-chemotherapy nausea and vomiting.[8]

Chronic low back pain affects millions of people globally, is commonly seen in primary care settings, and is often difficult to treat.[9,10] Chronic low back pain is defined as prolonged lower back pain for >12 weeks.[11] It is usually associated with movement limitation, reduced life quality, work productivity loss, and financial burden on healthcare institutions.[9,12] Chronic low back pain is a serious concern in Malaysia among several occupational groups.[13] Age, sex, body mass index, working posture, lifting heavy objects, lifestyle, working hours, and mental health have been identified as risk factors for lower back pain in Malaysia.[13] Chronic non-specific low back pain (cnLBP) occurs when no specific disease or structural pathology has been identified to explain the pain, and approximately 90% of chronic low back pain cases are non-specific.[11] Conventional cnLBP management includes non-pharmacological (activity modification, physical therapy, and psychological approach) and pharmacological (analgesic) approaches.[11] However, acupuncture has been used as a therapeutic approach for cnLBP in several countries. Notably, studies have found that acupuncture can alleviate symptoms and enhance physical function in individuals with cnLBP, and its beneficial effects might endure over time.[14-16]

The Theory of Planned Behaviour (TPB) is a psychological framework that aims to predict and understand human behaviour by considering individuals' attitudes, subjective

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norms, and perceived behavioural control.[17] These three factors collectively influence behavioural intentions, predicting actual behaviour. Therefore, by examining these factors, researchers can gain insights into the psychological determinants that impact health-related decisions and actions,[18,19] which are essential for designing interventions, enhancing the effectiveness of healthcare practices, and improving patient outcomes. cnLBP is a prevalent condition that significantly affects patients' quality of life and substantially burdens healthcare systems globally.[9,10,12] Acupuncture, a complementary medicine, has shown promise in managing cnLBP.[12,15,16] However, its acceptance and integration into mainstream medical practice remain inconsistent due to varying attitudes within the healthcare system and cultural perceptions in Malaysia. Acupuncture has roots in Malaysian society, particularly among the Chinese population; however, its recognition in the broader medical community faces challenges. Notably, some healthcare professionals remain skeptical, citing a lack of standardised training, limited experience with acupuncture, and insufficient evidence-based research. Additionally, limited exposure among other ethnic groups has led to hesitation in its adoption as a treatment option, slowing its incorporation into mainstream practice. Therefore, in this study, we aimed to determine medical practitioners' knowledge regarding the use of acupuncture for cnLBP and identify the factors influencing acupuncture referral for cnLBP under the TPB conceptual framework.

MATERIALS AND METHODS

Study design and setting

This cross-sectional observational study employed an online questionnaire based on the TPB Model framework to have an overview of medical practitioners' knowledge, attitudes, subjective norms, and perceived behavioural control regarding acupuncture referral for cnLBP. Data collection was conducted over 5 weeks between March 1, 2024, and April 5, 2024. The study targeted medical practitioners registered with the Malaysian Medical Association (MMA), which is the largest association representing Malaysia's medical community. Inclusion criteria were full registration with the Malaysian Medical Council (MMC) and active clinical practice as a medical practitioner. Therefore, medical practitioners with temporary MMC registration and medical students were excluded from the study.

Sampling method

Participants for this study were recruited using convenience sampling, with all registered MMA practitioners invited to participate through email. The invitation included a subject information sheet and a link to the questionnaire on Google Forms, with only those providing implied consent being able to proceed. The sample size was calculated using the Open Epi online calculator (https://www.openepi.com/Menu/OE_Menu.htm) based on a projected total of 10,000 registered MMA members and a reported 37% prevalence of complementary therapy referrals by medical professionals.[2] With a 95% confidence level and 5% margin of error, the calculated sample size for this study was 346 participants.

Research instrument

A newly developed, self-administered questionnaire was used to collect data based on the effectiveness of online surveys in reaching medical practitioners across a wide geographical area. This approach also enhanced accessibility, allowing participants to respond at their convenience and ensuring a diverse and representative sample.

The questionnaire included seven main sections. The first section was the demographic segment to collect personal and professional data (sex; age; years of clinical practice; area of expertise; practice entity; involvement in managing cnLBP; prior acupuncture experience, whether by training, self-experience, or referral; awareness of the T&CM Act's implementation; and acupuncture service facility in the workplace). The following six sections had 5–16 items each, designed to evaluate knowledge, attitudes, subjective norms, perceived behavioural control, intention, and action based on the TPB framework. Standard wording was used in these items, as recommended in the technical report Constructing a Theory of Planned Behaviour Questionnaire, to measure the TPB components.[20]

Responses for knowledge questions were "True," "False," or "Unsure." Furthermore, to assess the knowledge level, one mark was given for correct answers and zero for wrong and unsure answers. Knowledge level was classified based on total score percentiles; the lower two quartiles were "Very Poor" and "Poor," and the upper two quartiles were "Good" and "Excellent". TPB component responses used a 5-point Likert scale: "Agree," "Strongly Agree," "No Opinion," "Disagree," and "Strongly Disagree." AND "Never," "Rarely,"' "Sometimes," "Often," and "Always". The mean of the five responses for each item was calculated for analysis.

Questionnaire content was validated based on the items' relevance, clarity, simplicity, and ambiguity, and modifications were made according to experts' recommendations. Subsequently, the questionnaire underwent a pilot test to test its consistency and reliability using Cronbach's alpha before full-scale adoption. In addition, any shortcomings were addressed based on respondent feedback to finalise the questionnaire.

Data analysis

Data were analysed using the SPSS (version 27.0; IBM, Armonk, NY, USA). Numerical variables were expressed as means, standard deviations, medians, and interquartile ranges, while categorical variables were expressed as frequencies and percentages. Bivariate correlation and multiple regression analyses were applied to ascertain the relationship among knowledge level, attitudes, subjective norms, perceived behavioural control, intention, and action of acupuncture referral. Multiple regression analysis is suitable for a cross-sectional study based on the TPB framework because it allows for the assessment of the contributions of each TPB construct to predict behavioural intentions or actions while also controlling for confounding factors outside of the TPB framework. This enables a more accurate evaluation of how TPB and additional factors jointly influence the outcome. Statistical significance was set at P values <0.05.

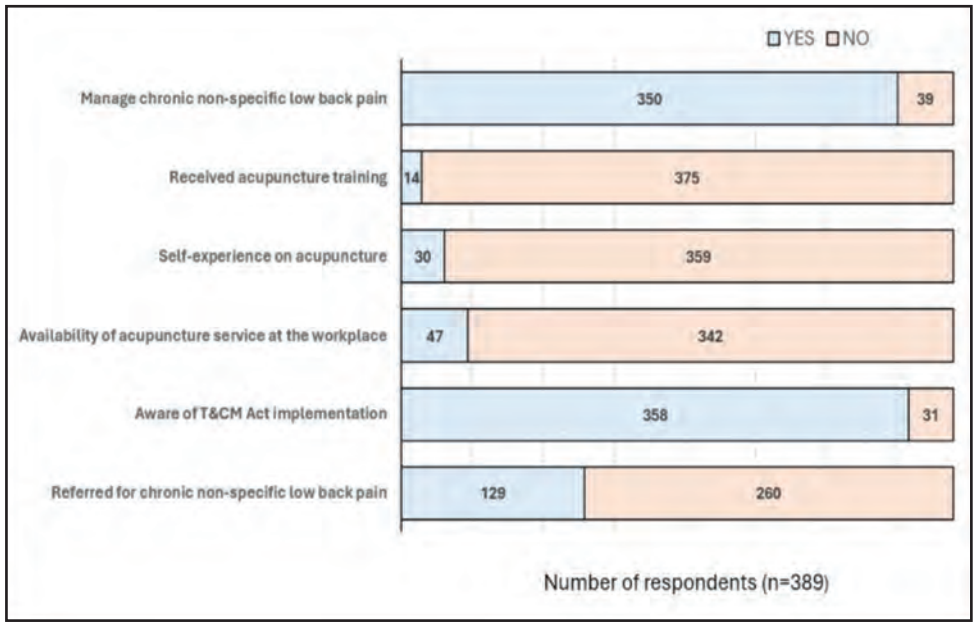

Fig. 1: Clinical characteristics (n=389)

Ethics approval and confidentiality
Participant anonymity was maintained throughout. The study was approved by the UNIMAS Medical Ethics Committee (UNIMAS/TNC(PI)/09 - 65/01 Jld.3 (29) and the IMU University Joint Committee for Research and Ethics (4.15/JCM-281/2024).

RESULTS

Respondent characteristics
In total, 389 medical practitioners responded to the questionnaire. The data were screened, and no missing values were found. The gender distribution showed a slight male predominance, with 217 male respondents (55.8%) compared to 172 female respondents (44.2%). The respondents' mean age was 42.0 years (standard deviation [SD]=7.9; range, 29–78 years). The mean practising years was 16.2 (SD=7.5; range, 2–50 years). Notably, most respondents (75.3%) were general practitioners (including medical officers at health clinics), and the remaining (24.7%) were specialists (family medicine specialists, 4.9%; medical-based specialists, 9.5%; and surgical-based specialists, 10.3%). The place of practice was predominantly in private clinics or hospitals, with 70.4% of respondents working in these settings. Table I shows the respondents' characteristics.

Clinical characteristics
Figure 1 illustrates clinical characteristics among 389 respondents, with a focus on managing cnLBP and their experience with acupuncture. A majority (90%) reported involvement in cnLBP management, yet only a small portion (3.6%) had formal training in acupuncture. Additionally, personal experience with acupuncture was limited, with just 7.7% of respondents having tried it themselves. Only 12.1% reported access to acupuncture services at their workplace, underscoring restricted availability in clinical settings. Awareness of the T&CM Act was notably high at 92%, suggesting a strong familiarity with regulatory guidelines for acupuncture. Despite this, only 33.2% had referred patients for acupuncture treatment for cnLBP, pointing to a gap between awareness of acupuncture's potential benefits and its practical application in patient referrals.

Factors affecting behavioural action for acupuncture referral for cnLBP treatment
Spearman's rho was used to measure the strength and direction of the relationship between the independent variables and behavioural actions for acupuncture referral (Table II). The percentage score of behavioural action for acupuncture referral showed a moderate positive correlation with received acupuncture training (ρ=0.12, $p<0.05$), acupuncture self-experience (ρ=0.18, $p<0.01$), attitude towards referral (ρ=0.19, $p<.01$), and perceived behavioural control (ρ=0.13, $p<0.05$), suggesting that training, personal experience, positive attitudes, and better perceived behavioural control were positively correlated with actual referral behaviours. The results also showed that the availability of acupuncture facilities in the workplace was positively correlated with the intention to refer patients for acupuncture treatment (ρ=0.11, $p<0.05$), suggesting that workplace service availability may influence referral intentions. Acupuncture knowledge, training, and self-experience were positively correlated with attitudes (ρ=0.11, $p<0.05$; ρ=0.15, $p<0.01$; and ρ=0.20, $p<0.01$, respectively) and perceived behavioural control (ρ=0.10, $p<0.05$; ρ=0.18, $p<0.01$; and ρ=0.16, $p<0.01$, respectively) among the respondents. These findings highlight the crucial role that knowledge, training, and personal experience play in shaping practitioners' attitudes and self-efficacy toward acupuncture referral.

There was a strong correlation between age and years of practice (ρ=0.97, $p<0.01$), indicating that their clinical experience also increased as practitioners aged. Additionally,

Table I: Respondent characteristics (n=389)

Characteristics	n	%
Sex		
Male	217	55.8
Female	172	44.2
Age in years		
< 35	50	12.9
35–44	223	57.3
45–54	92	23.7
≥55	24	6.2
Years of practice		
< 10	59	15.2
10–19	226	58.1
20–29	86	22.1
≥30	18	4.6
Type of practice		
General practitioner	293	75.3
Specialist	96	24.7
Place of practice		
Private clinic/hospital	274	70.4
Govt. clinic/hospital	115	29.6

Table II: Relationship between behavioural action for acupuncture referral for cnLBP and selected variables: Bivariate correlation analysis (n=389)

Parameters	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	--													
Sex	0.09	--												
Years of practice	0.97**	-0.09	--											
Manage cnLBP	-0.04	0.05	-0.01	--										
Received training	0.12*	-0.05	0.12*	-0.03	--									
Acupuncture self-experience	0.02	-0.07	0.01	-0.03	0.62**	--								
Acupuncture service availability	0.09	-0.04	0.09	0.07	0.10	0.01	--							
Aware of the T&CM Act implementation	-0.05	0.06	-0.06	0.28**	-0.10	-0.09	-0.01	--						
Attitude	0.07	-0.03	0.05	-0.04	0.15**	0.20**	0.04	0.03	--					
Subjective norms	-0.05	0.09	-0.04	0.10	0.09	0.05	0.00	0.01	0.09	--				
Perceived behavioural control	0.00	-0.01	0.01	0.02	0.18**	0.16**	0.06	-0.03	0.15**	0.06	--			
Acupuncture knowledge	0.01	0.07	-0.01	0.01	0.05	-0.03	0.02	0.07	0.11*	0.03	0.10*	--		
Intension to referral	0.06	0.07	0.07	0.05	0.09	0.13*	0.11*	-0.02	-0.01	0.09	0.04	-0.01	--	
Action of referral	0.01	0.08	0.02	-0.10	0.12*	0.18**	0.04	-0.03	0.19**	0.05	0.13*	0.05	0.07	--

*p<0.05, **p<0.01, ***p<0.001

Table III: Predictors of behavioural action for acupuncture referral for cnLBP: Multiple regression analysis (n=389)

Variables	Beta	SE	β	p-value	95% CI	
					LL	UL
(Constant)	0.560	19.949	-	0.978	-22.166	17.579
Age	-0.109	0.638	-0.044	0.864	-1.363	1.144
Sex	3.926	1.940	0.100	0.044*	0.285	7.892
Years of practice	0.136	0.672	0.052	0.840	-0.221	0.237
Acupuncture self-experience	11.051	3.739	0.151	0.003**	3.648	18.612
Acupuncture service availability at the workplace	1.816	2.943	0.030	0.538	-3.881	7.811
Aware of the T&CM Act implementation	-1.902	3.540	-0.026	0.591	-8.694	5.048
Acupuncture knowledge	0.012	0.048	0.001	0.829	-0.105	0.083
Attitude	0.282	0.075	0.189	0.001***	0.125	0.444
Subjective norms toward referral	0.092	0.084	0.054	0.276	-0.088	0.259
Perceived behavioural control	0.218	0.108	0.101	0.044*	0.023	0.436
Intention to refer for acupuncture	0.033	0.055	0.030	0.554	-0.076	0.133

*p<0.05, **p<0.01, ***p<0.001

years of practice were positively correlated with receiving acupuncture training (ρ=0.12, p<0.05), suggesting that more experienced practitioners were more likely to explore complementary therapies, such as acupuncture, to treat cnLBP. The awareness of the T&CM Act was moderately correlated with managing cnLBP (ρ=0.28, p<0.01), indicating that those aware of the Act were more likely to manage cnLBP using acupuncture.

Table III presents the bootstrap regression analysis examining the influence of various predictors on behavioural action for acupuncture referral. Acupuncture self-experience significantly impacted referral behaviour (β=0.151, p<0.01), highlighting the importance of personal acupuncture experience in influencing referral decisions. The finding suggests that practitioners with personal experience using acupuncture are more likely to refer patients for acupuncture treatment. Furthermore, attitudes towards acupuncture also significantly affected referral behaviour (β=0.189, p<0.001), indicating that more positive attitudes towards acupuncture were associated with increased referral actions. Perceived behavioural control was another significant predictor (β=0.101, p<0.05), suggesting that the more control practitioners felt over referring patients for acupuncture, the more likely they were to do so. Notably, there was no significant relationship between the subjective norms and acupuncture referral (β=0.054, p=0.276), suggesting that peer opinions did not directly influence the decision-making process for referring patients for acupuncture treatment. Furthermore, the regression analysis revealed that sex was statistically significant (β=0.100, p<0.05), indicating that sex differences influenced referral behaviour, with male practitioners being more likely to refer patients for acupuncture treatment. However, other demographic and professional characteristics, such as age, years of practice, availability of acupuncture service, awareness of T&CM Act implementation, and knowledge of acupuncture, did not show any significant relationship with referral behaviour for acupuncture treatment.

DISCUSSION

cnLBP is a highly prevalent condition that significantly impairs the quality of life for many individuals.[9,10] However, despite the availability of various treatment modalities, managing cnLBP remains a challenge in clinical practice.[11] Our results showed that a substantial majority of respondents (90.0%) are involved in managing cnLBP in their clinical practice. However, over time, medical practitioners may recognise the limitations of conventional methods in treating cnLBP, prompting them to explore complementary therapies. This may explain the positive correlation between years of practice and receiving acupuncture training (ρ=0.12, p<0.05) and that between managing cnLBP and the awareness of the T&CM Act's implementation (ρ=0.28, p<0.01). However, while there is high awareness of the T&CM Act (92.0%) and recognition of acupuncture as an approved T&CM modality (82.5%), the actual referral rate for acupuncture treatment remains considerably low at 33.2%. This discrepancy highlights the need for increased efforts to promote the acceptance and integration of acupuncture into cnLBP treatment protocols. Notably, most of those who made referrals were general practitioners (73.5%), predominantly male (59.7%). The significant relationship between sex and acupuncture referrals found in this study could be due to several factors. Male practitioners may feel more confident in recommending acupuncture, possibly due to cultural or social norms that make them more open to non-conventional treatments. They might also perceive acupuncture as lower risk or have more exposure to it through education or personal interest. Additionally, male practitioners may interpret patient needs differently, being more likely to see acupuncture as a beneficial option for cnLBP.

Understanding the medical practitioners' knowledge levels regarding specific therapies or health conditions is essential for improving treatment efficacy, patient outcomes, guideline adherence, and overall healthcare quality.[2,21,22] Herein, the general awareness and knowledge about acupuncture among medical practitioners were positive, with most respondents demonstrating a good understanding of the role of acupuncture in managing cnLBP. However, some misconceptions persist, which may hinder the referral process. Notably, some medical practitioners misunderstood or were uncertain about acupuncture procedures, such as whether local anaesthesia was required before acupuncture (17.7%), whether acupuncture needles worked by blocking the regional nerves (38.6%) and the safety of acupuncture in patients with diabetes (41.6%). Regarding the effectiveness of acupuncture in treating cnLBP, there was a misunderstanding or uncertainty regarding acupuncture needles soaked with herbs to gain analgesic effects (27.8%). These misunderstandings highlight the need for focused educational efforts. Notably, pre-congress workshops and interdisciplinary forums could serve as platforms to address these knowledge gaps. These educational initiatives would likely improve the understanding of medical practitioners and correct misconceptions, fostering a more favourable attitude towards acupuncture referral. Our findings align with previous studies that indicate a positive correlation between the level of knowledge and attitudes of practitioners towards their practice behaviour.[23-26]

Interestingly, the study also corroborated earlier research, showing that healthcare practitioners with a positive attitude toward complementary medicine are more likely to accept and incorporate it into their clinical practice.[27] This indicates that fostering positive attitudes through education and awareness campaigns could be pivotal in enhancing the integration of acupuncture and other complementary therapies. However, it is important to note that while there is a positive relationship between knowledge and attitudes, the study found no significant relationship between the level of knowledge and the actual referral action (β=0.001, p=0.829). This indicates that other factors, such as established clinical practices and the availability of institutional facilities, could influence the decision-making process. Similarly, previous studies have demonstrated that knowledge alone does not necessarily translate into action.[28,29] The gap between knowledge and actual practice highlights the importance of a well-planned process and the motivation to implement change. Notably, institutional support is crucial, suggesting that for integrative healthcare systems to develop effectively, education and knowledge must be paired with strong institutional backing. This combined approach could bridge

the gap between knowledge and practice, facilitating the integration of acupuncture into mainstream medical care.

Moreover, the study's findings were consistent with those of earlier studies, indicating that healthcare professionals with prior training and self-experience in complementary therapies, such as acupuncture, exhibit higher acceptance and integration rates of these therapies into their practice.[2,30,31] Training and self-experience help medical practitioners recognise the value of acupuncture and feel more confident in recommending it to patients. This emphasises the need to include complementary medicine subjects in undergraduate medical programs, giving students early exposure and practical experience with these treatment modalities. This educational strategy could create a new generation of medical practitioners who are more open to integrating complementary therapies into their practice.

Furthermore, we evaluated the perceived behavioural control in two aspects: self-efficacy and barrier. The results showed a moderate positive correlation between perceived behavioural control towards acupuncture referral (β=0.101, $p<0.05$). This is consistent with previous studies,[8,18,32] indicating that healthcare practitioners were more likely to perform behavioural actions when they had higher perceived behavioural control. Practitioners who feel confident and have the necessary resources, support, and knowledge to refer patients to acupuncture are more likely to do so. However, despite the positive perceived behavioural control towards acupuncture referral, barriers are preventing its broader adoption. Notably, concerns about the lack of scientific evidence supporting acupuncture (53.0%) and the quality of acupuncturists (63.0%) were major deterrents. These concerns highlight the need for stronger research and collaboration between modern and complementary medicine professional bodies. Healthcare providers should prioritise enhancing education and training, promoting scientific evidence, and raising awareness of relevant policies, such as the T&CM Act.

Additionally, establishing clear referral systems and supportive institutional policies will facilitate the integration of acupuncture into conventional medical practice. Strategies to overcome existing barriers include streamlining referral processes, reducing paperwork, providing directories of acupuncturists, and educating patients about the benefits of acupuncture in managing cnLBP. We found that many respondents (81.2%) expressed interest in learning more about acupuncture as a treatment option for cnLBP. However, confidence in identifying suitable patients for acupuncture treatment was relatively low, with only 28.1% of practitioners feeling assured in their ability to do so. This gap highlights the need for more continuous medical education programs and professional development modules focused on enhancing knowledge and confidence in selecting suitable patients with cnLBP for acupuncture treatment.

Finally, we found no significant correlation between subjective norms and the action to refer patients with cnLBP for acupuncture treatment (β=0.054, p=0.276). This indicates that the opinions and expectations of colleagues, peers, and the broader medical community may not strongly influence individual practitioners' choices to recommend acupuncture. This finding is consistent with previous research, which has identified subjective norms as a weak predictor of behavioural actions.[27,32,33] Notably, several factors may explain this result. First, practitioners may rely more on their own clinical experience and training than the opinions of others. Second, the perceived lack of scientific evidence supporting acupuncture could lead practitioners to prioritise their own judgment or institutional guidelines over peer influence. Third, time constraints in busy clinical settings may prompt practitioners to make independent decisions, minimising the role of social or professional expectations. Ultimately, this suggests that personal attitudes and clinical autonomy are likely stronger drivers in the decision to refer patients for acupuncture than subjective norms.

This study has several strengths and some limitations. As the first investigation into Malaysian medical practitioners' behavioural actions regarding acupuncture referrals for cnLBP, it provides valuable insights into the complex relationships among predictors, intentions, and actions in this decision-making process. Furthermore, the study's findings contribute to the understanding of areas for improvement in healthcare integration and patient care optimisation. Furthermore, the recruited participants (n=389) exceeded the calculated sample size of 346, which enhanced the reliability and statistical power of the findings.

However, the limitations of this study include potential bias from convenience sampling of a single association's members, which may affect generalizability to the broader population of Malaysian medical practitioners. The cross-sectional study design also poses a limitation in establishing causality. The use of a self-administered online questionnaire offered advantages such as cost-effectiveness, wide reach, and convenience; however, it also presented challenges. Online surveys can reach diverse audiences and potentially increase participation rates through anonymity and convenience; however, they may exclude certain demographics (senior practitioners) owing to technological barriers, potentially skewing the sample. Additionally, the lack of supervision in online surveys may lead to lower-quality data due to hurried responses.

CONCLUSION

This study reveals significant relationships between various factors and medical practitioners' acupuncture referral behaviours for cnLBP. Personal experience with acupuncture, positive attitudes, and higher perceived behavioural control were associated with increased referral rates, while the availability of acupuncture facilities in the workplace positively influenced referral intentions. Notably, greater acupuncture knowledge was associated with more favourable attitudes and higher perceived behavioural control. These findings have important implications for medical education and healthcare policy. Therefore, incorporating acupuncture education into medical training can foster more informed attitudes and boost practitioners' confidence in recommending it as a treatment option. Hands-on experience or exposure to acupuncture in clinical settings could further enhance referral behaviours. From a policy perspective, improving access to acupuncture services in

healthcare facilities may promote its wider use, particularly for managing cnLBP.

Future research could explore sex differences in referral behaviours, examining whether male and female practitioners differ in their attitudes, personal experience, or perceived control when referring patients for acupuncture. Additionally, qualitative studies could investigate barriers preventing practitioners from acting on their intention to refer, such as lack of institutional support or patient-related concerns. A comparative analysis of referral patterns between private and public sector practitioners could also provide insights into how different healthcare settings and policies influence referral behaviours and whether disparities in access to acupuncture services exist.

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CONFLICT OF INTEREST

All authors declare that there are no competing interests associated with this study.

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ORIGINAL ARTICLE

A decade of intracapsular cataract extraction: clinical profile and visual outcomes at Hospital Melaka, Malaysia

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ABSTRACT

Introduction: Cataract is a leading cause of visual impairment globally and in Malaysia, with surgery being the definitive treatment. While intracapsular cataract extraction (ICCE) is now less commonly performed due to advancements in surgical techniques, it remains essential in specific cases, such as those with weak zonular support. This study aims to evaluate the incidence, clinical profiles, and visual outcomes of patients who underwent ICCE, with or without intraocular lens (IOL) implantation, at Hospital Melaka, Malaysia, over the past decade.

Materials and Methods: A retrospective review was conducted on patients who underwent ICCE at Hospital Melaka, Malaysia, from January 2014 to December 2023.

Results: A total of 143 ICCE surgeries were performed on 135 patients. Most patients were male (n=88, 65.2%), with females comprising 34.8% (n=47). Most surgeries were performed on patients aged 60–69 years (n=48, 35.5%), followed by those aged 50–59 years (n=31, 23.0%) and 70–79 years (n=28, 20.7%). Incidence was lower among patients below 50 years and above 80 years. In terms of ethnicity, the highest incidence was among Malays (n=77, 57.0%), followed by Chinese (n=42, 31.1%) and Indians (n=15, 11.1%).

The leading cause of ICCE was senile cataract with weak zonular support (n=58, 40.6%), followed by trauma (n=33, 23.1%), intraoperative complications (n=30, 21.0%), congenital cataracts (n=14, 9.8%), pseudoexfoliation (n=4, 2.8%), and lens-induced glaucoma (n=4, 2.8%).

Post-surgery, 76 patients (53.1%) were left aphakic. Among those receiving IOL implants, 21.0% (n=30) had anterior chamber IOL, 14.7% (n=21) received an iris-claw IOL, and 11.2% (n=16) had a scleral-fixated IOL. Twelve weeks after IOL implantation, 60.9% (n=39) achieved good visual acuity of 6/12 or better, while 17.2% (n=11) had moderate vision (6/18 to 6/36), and 21.9% (n=14) had poor vision (worse than 6/60).

Conclusion: The incidence of ICCE was low, accounting for only 0.66% of the 21,596 cataract surgeries performed at Hospital Melaka, Malaysia, during the study period. The primary indication was senile cataracts with weak zonular support. Most patients achieved favourable visual outcomes at 12 weeks postsurgery following IOL implantation, with the iris-claw IOL showing superior postoperative visual results compared to other IOL types.

KEYWORDS:
Intracapsular cataract extraction, cataract, visual outcomes, intraocular lens, aphakia

INTRODUCTION

Cataract remains one of the leading causes of visual impairment and blindness globally, including in Malaysia. Although cataracts primarily affect the elderly, they can also manifest in early childhood due to intrauterine infections, chromosomal abnormalities, or metabolic disorders.[1,2] Trauma is another significant factor contributing to cataract development. According to the National Eye Survey, 39.11% of bilateral blindness cases in Malaysia are attributed to cataracts.[2] Fortunately, cataract-induced blindness is preventable with cataract surgery, which remains the most frequently performed refractive procedure in government hospitals across Malaysia and worldwide.

Cataract surgery techniques have evolved substantially, progressing from intracapsular cataract extraction (ICCE) to extracapsular cataract extraction (ECCE) and, more recently, to phacoemulsification. The choice of surgical approach depends on the patient's visual needs and eye condition, as each technique carries distinct indications and associated risks.[3] While ICCE is less commonly performed in high-income countries compared to ECCE or phacoemulsification, it remains a viable option in low and middle-income settings, especially where other methods are not feasible.[4] During ICCE, various intraocular lenses (IOLs) may be implanted in different anatomical locations, such as the anterior chamber, iris-claw, or scleral-fixated positions. However, ICCE is associated with a higher risk of complications, such as endophthalmitis, which has led to its decreased use, although it is still indicated in cases with weak zonules or other specific conditions.

This study aims to evaluate the incidence, clinical profiles, and visual outcomes of patients who underwent ICCE, with or without IOL implantation, at Hospital Melaka over the past decade.

MATERIALS AND METHODS

This retrospective study analysed ten years of data from

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Table I: Clinical profile of patients who underwent intracapsular cataract extraction (ICCE)

	Frequency, n (%)
Gender	
Male	88 (65.2)
Female	47 (34.8)
Age (Years Old)	
1 - 9	4 (3.0)
10 - 19	2 (1.5)
30 - 39	5 (3.7)
40 - 49	5 (3.7)
50 - 59	31 (23.0)
60 - 69	48 (35.5)
70 - 79	28 (20.7)
>80	12 (8.9)
Race	
Malay	77 (57.0)
Chinese	42 (31.1)
Indian	15 (11.1)
Non-Malaysian	1 (0.74)
Aphakia	76 (53.1%)
Types of IOL	
a. AC IOL	30 (21.0%)
b. Iris claw IOL	21 (14.7%)
c. Scleral fixated IOL	16 (11.2%)

Abbreviations: IOL: intraocular lens; AC IOL: anterior chamber intraocular lens

Table II: Visual acuity post-operative with and without intraocular lens implantation

Lens status	6/6 to 6/12	6/18 to 6/36	6/60 and worse	Missing data
Aphakia	0 (0%)	7 (9.2%)	57 (75.0%)	12 (15.8%)
AC IOL	17 (56.6%)	5 (16.7%)	6 (20.0%)	2 (6.7%)
Iris-claw IOL	16 (76.2%)	5 (23.8%)	0 (0%)	0 (0%)
Scleral-fixated IOL	6 (37.5%)	1 (6.25%)	8 (50.0%)	1 (6.25%)

Abbreviations: IOL: intraocular lens; AC IOL: anterior chamber intraocular lens

patients who underwent ICCE at Hospital Melaka, Malaysia, between January 2014 and December 2023. Data were sourced from the National Eye Database (NED), which includes the Cataract Surgical Registry. The study adhered to the principles of the Declaration of Helsinki and received approval from the Malaysian Medical Research Ethics Committee (NMRR ID-24-02322-FYK (2)). Data collection was facilitated by doctors assisting in the operating theatres at Hospital Melaka, Malaysia. Hospital Melaka is a government-funded public hospital that serves as a referral centre for patients from primary care facilities and private hospitals in Melaka and northern Johor. It also serves as a teaching hospital for Melaka Manipal Medical College medical students.

This study included all patients who underwent ICCE, with or without IOL implantation, between January 2013 and December 2023. Data collected encompassed patients' clinical profiles, including age, gender, ethnicity, indications for surgery, type of IOL implantation, and visual outcomes. The World Health Organization (WHO) established the International Classification of Diseases 11 (2018) criteria for visual impairment. According to these standards, visual acuity is categorised as follows: good vision (6/6 to 6/12), moderate visual impairment (6/18 to 6/60), and poor vision (worse than 6/60). Patients who underwent phacoemulsification or ECCE were excluded from the study.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, version 29.0. Categorical variables are presented as frequencies and percentages. Descriptive analysis was used to summarise the data. The Wilcoxon Signed Ranks test was employed to compare pre-and postoperative visual acuity, measured in LogMAR, for each type of IOL.

RESULTS

A total of 143 ICCE surgeries were performed on 135 patients at Hospital Melaka from 2014 to 2023. The incidence of ICCE was notably low, with only 143 cases (0.66%) out of 21,596 cataract operations. The majority of cases involved male patients and those of Malay ethnicity, with the highest incidence of ICCE surgeries occurring in patients aged 60 to 69 years (Table I). Senile cataracts with weak zonular support were the leading cause of ICCE among male patients, followed by trauma and intraoperative complications (Figure 1 and Figure 2). Post-operatively, more than half of the patients (53.1%) remained aphakic. In contrast, the others received various intraocular lens implants, including anterior chamber IOLs, iris-claw lenses, and scleral-fixated lenses (Table I).

Figure 3 illustrates the best corrected visual acuity (BCVA) outcomes in LogMAR before and after surgery for different types of IOL implants, excluding cases of aphakia. Visual outcomes 12 weeks post-surgery were favourable in patients with primary IOL implantation, with the iris-claw IOL group showing the best results, followed by anterior chamber and scleral-fixated IOLs. Patients left aphakic generally had poorer outcomes.

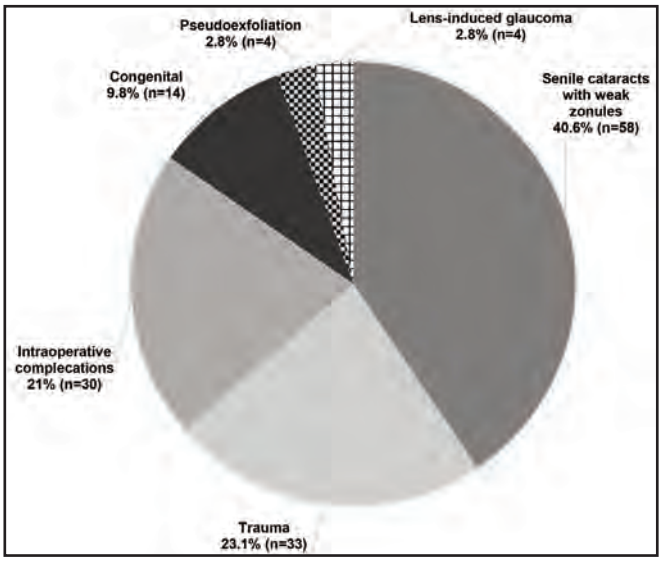

Fig. 1: Indications for intracapsular cataract extraction surgery

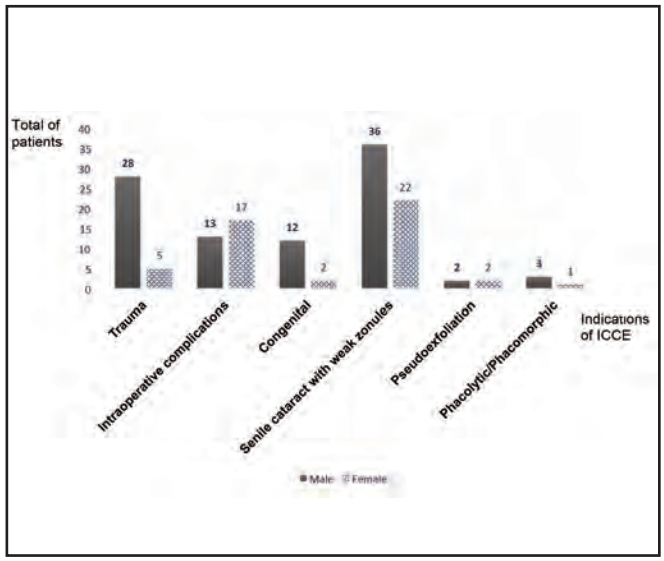

Fig. 2: Indications for intracapsular cataract extraction categorised by gender
Abbreviation: ICCE: intracapsular cataract extraction

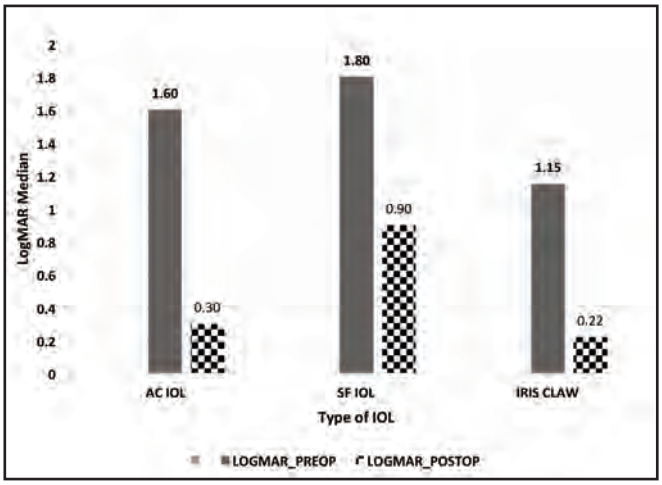

Fig. 3: Pre- and Post-Operative Visual Acuity (LogMAR) by Type of Intraocular Lens
Abbreviations: AC IOL: anterior chamber intraocular lens; SF IOL: scleral fixated intraocular lens; IOL: intraocular lens, LogMAR: Logarithm of the Minimum Angle of Resolution

Tables I and II summarise further details of patient demographics, causes, and visual outcomes, with Figures 1–3 illustrating key surgical indications and postoperative visual acuity.

DISCUSSION

This study offers valuable insights into the outcomes of ICCE surgeries conducted at Hospital Melaka from 2014 to 2023. Among the 143 ICCE surgeries performed, the leading cause was senile cataracts with weak zonular support, particularly in patients aged 60 to 69 years. Weak zonules often necessitate ICCE over other cataract surgery techniques, such as ECCE or phacoemulsification, due to an increased risk of complications such as posterior capsule rupture or vitreous loss.[5] These complications prolong surgical time, elevate the risk of retinal detachment, and impair proper IOL placement, frequently resulting in aphakia or necessitating anterior chamber IOL placement.

Our findings align with Berler et al.[6], who reported that older cataract patients, particularly those over 88 years, experience higher complication rates, including posterior capsule tears and poorer visual outcomes, than younger patients.[6] In our cohort, a significant portion of patients with weak zonular support underwent ICCE, highlighting the importance of early detection of zonular instability and the potential role of capsular support devices in improving outcomes.

Male patients comprised the majority of ICCE cases, with trauma being a significant contributing factor, particularly among those aged 50 to 59 years. This finding is consistent with studies by Özbilen et al.[7], as well as Wong et al.[8], both of which reported a higher incidence of traumatic cataracts in men, often resulting from motor vehicle accidents and sports injuries.[7,8] Mariya et al.[9] stated that there is a higher incidence of traumatic cataracts in males due to their involvement in outdoor activities and sports.[9] Our study further supports these findings, with 19.6% of male patients undergoing ICCE due to trauma. However, types of trauma are not further evaluated. Given the substantial impact of trauma on male patients, especially those of working age, public health efforts should focus on prevention, particularly in high-risk occupations and environments.

In paediatric patients, congenital diseases, such as Marfan's syndrome, accounted for 9.8% of cases. This is consistent with previous studies indicating that systemic disorders like Marfan's syndrome, homocystinuria, and sulfite oxidase deficiency are associated with lens subluxation due to zonular weakness.[10] However, Kabylbekova et al.[11] have highlighted Down syndrome as the most common syndrome associated with cataracts.[11] Our study identified Marfan's syndrome as the predominant congenital condition in paediatric ICCE cases, emphasising the need for early diagnosis and appropriate surgical intervention in these patients.

A significant proportion of patients in this study were left aphakic post-ICCE (53.1%), particularly those in the 60 to 69 age group. Aphakia, in these cases, may have been planned, with secondary IOL implantation intended, but patients failed to return for follow-up. Barriers to follow-up may include socioeconomic challenges, transportation difficulties, or a lack of understanding about the importance of further treatment. This finding underscores the need for improved postoperative care and patient education to ensure optimal visual rehabilitation.

Postoperatively, patients with IOL implantation demonstrated better visual outcomes compared to those left aphakic. Among aphakic patients, 9.2% (n=7) had a BCVA between 6/18 and 6/36. In contrast, 58.2% (n=39) of patients who received IOL implants achieved good visual acuity, with vision of 6/12 or better. Notably, the iris-claw IOL provided superior visual outcomes compared to AC IOL and scleral-fixated IOLs. This could be attributed to the younger age of patients receiving iris-claw IOLs, which may contribute to better postoperative results. Additionally, the stability offered by iris-claw IOLs, particularly in patients with Marfan's syndrome, makes them a preferred option over scleralfixated IOLs, as shown by studies like Al-Dwairi et al.[14] and Muthukumar et al.[15]

Patients who underwent ICCE or ECCE faced a significantly higher risk of postoperative BCVA of 6/18 or worse compared to those who had phacoemulsification, primarily due to increased postoperative astigmatism, discomfort, and slower visual recovery.16 This underscores the importance of innovating surgical techniques, especially for complex cases requiring ICCE.

Aphakic patients need thorough visual prognosis assessments before secondary IOL implantation, with temporary corrective lenses improving their quality of life while awaiting implantation. Post-ICCE refractive monitoring is vital to address high astigmatism from sutures. Factors like intraoperative complications, surgeon experience, and operation time significantly influence visual outcomes, emphasising the need for skilled surgeons and efficient procedures to reduce risks such as posterior capsule rupture or prolonged inflammation. Enhancing follow-up rates through community outreach and rehabilitation programs can improve postoperative care, particularly for remote patients. Limitations, such as the absence of long-term follow-up data and variability in surgeon expertise, highlight the need for future research on extended outcomes, IOL types, less invasive trauma case alternatives, and improved postoperative care to optimise ICCE results.

CONCLUSION

In conclusion, ICCE accounted for a small fraction of cataract surgeries performed at Hospital Melaka, with senile cataracts and weak zonular support being the predominant causes. Notably, ICCE represented only 0.66% of the 21,596 cataract surgeries conducted during the study period. Trauma was a significant contributor, especially among male patients. Although patients with IOL implants generally experienced better visual outcomes, those left aphakic faced greater difficulties in achieving good vision. Patients with iris-claw IOLs, particularly those with Marfan syndrome, showed positive visual results postoperatively. Strengthening postoperative care, particularly in follow-up and rehabilitation, is essential. Further studies are needed to evaluate alternatives to ICCE and to better understand long-term outcomes, especially for aphakic patients.

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ORIGINAL ARTICLE

Effectiveness of a developed module in improving quality of life among breast cancer patients undergoing chemotherapy at Institut Kanser Negara

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ABSTRACT

Introduction: Cancer is one of the leading causes of morbidity and mortality worldwide. Breast cancer risk has risen due to lifestyle choices and genetic factors. Women with breast cancer symptoms experience lower quality of life (QoL), particularly in psychological and physical domains, compared to healthy women. Several studies reveal that poor QoL among breast cancer patients increases the risk of psychological distress. This study aimed to develop, implement, and evaluate the effectiveness of a counselling module in improving the QoL among breast cancer patients undergoing chemotherapy at the Institut Kanser Negara (IKN).

Materials and Methods: A single-blinded Randomized Controlled Clinical Trial was conducted at the IKN between January 2023 and June 2023. The estimated sample size was 120 participants. A sequential numbering system assigned a unique identifier to each participant until a total of 120 participants were recruited, with 60 participants in both the intervention and control groups. The intervention group received chemotherapy counselling using a newly developed module. QoL and depression were assessed at multiple time points using a validated questionnaire. Data were analysed using SPSS version 26, with independent tests and two-way repeated measures ANOVA. A p-value < 0.05 was considered significant, and partial eta squared was used to measure effect size.

Result: Overall, in age distribution, the intervention group had the highest percentage of participants in the 41-60 years category (40.0%), whereas the control group had the highest percentage of participants aged ≥61 years (38.3%). The counselling module was effective in improving QoL and depression among participants at baseline and for three consecutive follow-ups following interventions. The QoL showed improvement in all four domains in the intervention group, which were Physical Health (p < 0.001), Psychological (p < 0.001), Social Relationship (p < 0.001), and Environment (p = 0.001). There was also a moderate effect reduction on depression (p < 0.001).

Conclusion: The newly developed counselling module was effective in improving the QoL and depression among breast cancer patients. Repetitive counselling sessions by pharmacists, which were conducted during the module implementation, played a key role in ensuring the well-being of breast cancer patients throughout the treatment journey.

KEYWORDS:
Cancer, chemotherapy, breast cancer, quality of life, depression

INTRODUCTION

Cancer, known as malignant tumors and neoplasms, occurs due to the uncontrolled growth of abnormal cells in the body.[1] It is one of the primary contributors to global mortality, responsible for nearly 10 million deaths in 2020.[2] That year, breast cancer diagnoses reached 2.3 million among women globally, resulting in 685,000 deaths. By the end of 2020, 7.8 million women who had been diagnosed with breast cancer in the previous five years were still alive, making it the most widespread cancer worldwide. Developed countries see higher breast cancer rates, and the incidence is rising almost everywhere.[1]

In Malaysia, cancer prevalence has risen over the past decade (2007-2016) among both men and women.[3] According to 2022 data from Global Cancer Observatory (GLOBOCAN), breast cancer accounted for the highest proportion (16.2%) of all new cancer cases in Malaysia, with 8,371 new cases diagnosed that year.[4] The Malaysian National Cancer Registry reported 115,238 new cancer cases between 2012 and 2016. Despite advanced health facilities, Malaysia's cancer mortality rate remains high. Breast cancer is the leading cause of cancer deaths among women in Malaysia, with the highest prevalence recorded among the Chinese ethnic population.[4] Chemotherapy, often combined with radiation or surgery, is the most common treatment for breast cancer.[5] Despite its benefits for survival, chemotherapy causes significant side effects, particularly impacting psychological health and physical well-being.[6,7]

Quality of life is a key measure of quality care in oncology.[8] Women with breast cancer symptoms experience lower QoL, particularly in psychological and physical domains, compared to healthy women.[9] Increased psychological distress negatively impacts illness perception and body

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image.[10-12] Chemotherapy can further decline QoL and psychological health. Iddrisu et al. (2020) noted that some patients defaulted on their next chemotherapy cycle due to the disruptive effects on their daily routine.[13] Depression is a common psychological effect of chemotherapy among breast cancer patients, affecting about 20% of women.[14-16] Depression leads to emotional distress and significantly reduces QoL.[17-18]

Educational counselling has been shown to effectively manage cancer patients and mitigate some negative consequences of chemotherapy.[19] Iddrisu et al. (2020) recommended educating breast cancer patients on coping strategies and lifestyle activities to aid their recovery.[13] However, there are limited studies on educational interventions among breast cancer patients in Malaysia. This study aimed to develop, implement, and evaluate the effectiveness of a counselling module to improve the QoL of breast cancer patients undergoing chemotherapy at Institute Kanser Negara (IKN).

MATERIALS AND METHODS

Study Design and Setting

A randomised controlled trial (RCT) with a single-blinded study design was used in the study. This study was carried out at IKN. Participants were recruited from the oncology ward at the IKN. Eligible patients met the following criteria: (i) aged above 18; (ii) undergoing chemotherapy at the IKN; (iii) able to communicate verbally. Patients with language barriers or severe illnesses were excluded. The patients were randomly assigned into 2 groups by the pharmacist on duty for the day. The 2 groups consisted of the intervention group and control group. A total of 120 participants were randomly selected and allocated into intervention and control groups using a randomization method based on odd and even numbers, with each group consisting of 60 participants. The control group adhered to the standard IKN counselling protocol for breast cancer patients undergoing chemotherapy, while the intervention group received quality-of-life counselling using a specific module developed by a pharmacist. Data collection at IKN spanned six months, from January 2023 to July 2023. Counselling sessions for the intervention group began during their initial visit and continued through the first cycle of chemotherapy, with ongoing sessions up to the third follow-up appointment. Following a single-blinded approach, both groups were kept unaware of their assigned group. The effectiveness endpoints were evaluated over three consecutive chemotherapy cycles, with varying time intervals between each cycle ranging from 3 to 6 weeks. The study flow is depicted in Figure 1. A validated, pretested questionnaire was used to measure the QoL and depression at baseline, first follow-up, second follow-up, and third follow-up. Data were analysed using SPSS version 26. Independent tests were used to compare the variables at baseline. Two-way repeated measures ANOVA tests were used to assess the effectiveness of the intervention. A p-value of less than 0.05 was considered significant and partial eta squared was used to measure effect size.

Intervention module

The newly developed intervention module, 'Improving Quality of Life in Breast Cancer Patients Undergoing Chemotherapy,' integrates components of QoL and Depression. The final version of the module was established after a pilot test conducted with breast cancer patients undergoing chemotherapy treatment, followed by a comprehensive review and revision by a panel of experts. The module provides an overview of key topics related to breast cancer and chemotherapy treatment. Chapter One covers the basics of breast cancer, chemotherapy, and dietary recommendations. Chapter Two focuses on chemotherapy drugs and their potential side effects. Chapter Three addresses managing physical side effects of chemotherapy, while Chapter Four discusses non-pharmacological techniques for coping with symptoms of depression. The primary objective of this module is to alleviate the depression levels experienced by breast cancer patients, ultimately improving their overall QoL. The module was implemented through repetitive pharmacist counselling following each cycle of chemotherapy for patients in the treatment group. Each counselling session lasted approximately 30-40 minutes per patient. These counselling sessions were conducted by pharmacist individually and face-to-face with patients, typically at their bedside, known as bedside counselling. Meanwhile, patients in the control group received counselling sessions using the hospital's existing counselling practices

Questionnaire

This study employed a questionnaire consisting of sociodemographic data, including age, race, education, income, marital status, and cancer stage. The World Health Organization Quality of Life Brief Version (WHOQOL-BREF) questionnaire to assess the patient's QoL, comprising four domains: physical health, psychological, and social relationships, and environment. Each question in WHOQOL-BREF was scored from one to five, with higher scores indicating better evaluation. For depression assessment, the Patient Health Questionnaire (PHQ-9) was utilised, consisting of nine items derived from DSM-IV Criteria for Major Depressive Disorder. The PHQ-9 has demonstrated good sensitivity and specificity in detecting depression. These questionnaires were validated among the Malaysian population and are available in English and Malay languages.

Data analysis

The data were entered into the statistical program SPSS version 26 (IBM SPSS Statistics 26, 2019). Analysis was done using descriptive and inferential statistical methods. An independent samples t-test was conducted to evaluate baseline differences between the intervention and control groups, as well as to compare changes in QoL domains and depression scores between the groups across the baseline, 1st counselling, 2nd counselling, and 3rd counselling sessions. The analysis of variance (ANOVA) test was utilised to examine the primary and interaction effects within and between groups concerning the average scores of QoL and depression. An analysis was undertaken to compare group times using multiple pairwise comparisons, which were conducted with a predetermined level of significance, denoted as alpha (α), set at 0.05 using the Bonferroni correction. This study's confidence interval (CI) was established at a 95% level, with a significance level of 0.05.

Ethical consideration

The ethical clearance for this study was obtained from the Medical Research and Ethics Committee (MREC) NMRR-20-3209-54195 (IIR), Ministry of Health Malaysia, and IKN. Each patient has distributed an information sheet about the study before data collection. Participants' participation was voluntary, and informed consent was obtained from them before the conduct of the study.

RESULTS

Table I shows the baseline socio-demographic characteristics of both the intervention and control groups. In the age distribution analysis, the intervention group had the highest percentage of participants in the 41-60 years category (40.0%), whereas the control group had the highest percentage of participants aged ≥61 years (38.3%). Approximately 51.0% of participants in both groups identified as Chinese. Most participants in the intervention group (52.2%) and the control group (47.8%) were married. Regarding education levels, the majority of participants in the intervention group (56.6%) had no formal education or only primary education, while 43.2% had secondary education and 47.8% had tertiary education. In the control group, a higher percentage had secondary education (56.8%) compared to those with no formal/primary education (43.3%) and tertiary education (52.2%). Employment status was similar between groups, with 52.0% of participants in the intervention group and 48.0% in the control group being employed. Most households in both groups reported an income of less than RM 2,000.00. Most participants in both groups were in stage 2 of cancer and were undergoing their second and third cycles of chemotherapy. Many participants expressed concerns about chemotherapy-related pain and adverse effects, and most did not participate in cancer support groups. These characteristics were comparable between the two groups, with no statistically significant differences observed. Consequently, prior to the introduction of the intervention module, both groups displayed similar outcome measures.

Effectiveness of the Newly Developed Intervention Module on Quality of Life

Table II compares the mean scores for QoL and each domain between the intervention and control groups at baseline until the 3rd follow-up. At baseline, there were no statistically significant differences between physical health (p = 0.502), psychological (p = 0.260), social relationships p = 0.225), and environment (p = 0.725) between the intervention and control groups. Initially, there were no statistically significant differences in mean QoL ratings for Physical Health, Psychological Health, Social Relationships, and Environment between the intervention and control groups at baseline. For Physical Health, the intervention group showed a significant increase in mean scores at the first follow-up (M = 71.92, SD = 14.81), continuing to improve in the 2nd (M = 76.62, SD = 15.02) and 3rd (M = 79.30, SD = 14.63) follow-ups, remaining significantly higher than both baseline and control group levels (mean difference = 1.82, 95% CI = -3.53, 7.16, p = 0.502).

For Psychological Health, the intervention group exhibited significant improvement at the first follow-up (M = 60.92, SD = 15.27), with further positive changes in the 2nd (M = 63.00, SD = 14.89) and 3rd (M = 65.55, SD = 18.37) follow-ups. In contrast, the control group showed a significant decrease in mean Psychological Health scores from the first follow-up (M = 52.03, SD = 17.79) (mean difference = -3.35, 95% CI = -8.34, 1.63, p = 0.185).

For Social Relationships, the baseline differences were not statistically significant (mean difference = -5.31, 95% CI = -13.02, 2.40, p = 0.176). However, the intervention group showed a substantial improvement at the first follow-up (mean difference = -15.13, 95% CI = -22.7, -7.56, p < 0.001), which continued to the 2nd (mean difference = -27.6, 95% CI = -34.71, -20.48, p < 0.001) and 3rd follow-ups (mean difference = -33.47, 95% CI = -40.52, -26.42, p < 0.001).

For the Environment, no significant differences were noted at baseline (mean difference = -0.97, 95% CI = -4.46, 6.39, p = 0.725). However, significant improvements were seen in the intervention group at the first follow-up (M = 71.97, SD = 18.75), 2nd (M = 75.15, SD = 16.54), and 3rd follow-ups (M = 77.85, SD = 15.11). In contrast, the control group showed a significant decrease from the first follow-up (M = 54.57, SD = 17.45) onwards. Overall, the intervention group exhibited significant and sustained improvements across all QoL domains compared to the control group, highlighting the effectiveness of the intervention.

In Table III, the results of the two-way repeated measures ANOVA analysis for each domain of QoL on both groups (intervention and control) and time (baseline until 3rd follow-up) effects and interaction between group and time showed that; in physical health, there were significant main effects for the group (F (1, 118) = 22.952, p < 0.001, partial η2 = 0.163), Time (F (3, 182.940) = 10.472, p < 0.001, partial η2 = 0.082), and the interaction between group and time (F (1.550, 182.940) = 61.446, p < 0.001, partial η2 = 0.342); in psychological, there were significant main effects for group (F (1, 118) = 58.937, p < 0.001, partial η2 = 0.333), time (F (1.555, 183.542) = 5.181, p = 0.012, partial η2 = 0.042), and the interaction between group and time (F (1.555, 183.542) = 63.878, p < 0.001, partial η2 = 0.351). Regarding social relationship, there were significant main effects for group ((F (1, 118) = 44.860, p < 0.001, partial Ƞ2 = 0.275); time (F (1.678, 198.038) = 10.465, p < 0.001, partial Ƞ2 = 0.081); and interaction between group and time (F (1.678, 198.038) = 173.392, p < 0.001, partial Ƞ2 = 0.595). Finally, in environment also, there were significant main effects for group Group (F (1, 118) = 65.327, p <0.001, partial Ƞ2 = 0.356), time (F (1.872, 226.248) = 7.174, p = 0.001, partial Ƞ2 = 0.057), and the interaction between group and time (F (1.872, 226.248) =129.437, p = <0.001, partial Ƞ2 = 0.523).

Effectiveness of the Newly Developed Intervention Module on Depression

Table IV compares the mean scores for depression between the intervention and control groups at baseline until 3rd follow-up. At baseline, there were no significant differences in depression (p = 0.749) between the intervention and control groups. Initially, no statistically significant differences in

Table I: Baseline comparison of socio-demographic characteristics between the intervention and control groups (n=120)

Characteristics	Frequency, n (%)		Total	Chi-square value	p-value
	Control group n=60	Intervention group n=60			
1. Age					
≤40	15(42.9)	20(57.1)	35	2.058	0.357
41-60	22(47.8)	24(52.2)	46		
≥ 61	23(59.0)	16(41.0)	39		
2. Race					
Malay	21(45.7)	25(54.3)	46	1.491	0.684
Chinese	31(51.7)	29(48.3)	60		
Indian	7(53.8)	6(46.2)	13		
Others	1(100)	0(0)	1		
3. Marital Status					
Single	14(53.8)	12(46.2)	67	1.214	0.545
Married	35(52.2)	32(47.8)	26		
Widowed/Divorced	11(40.7)	16(59.3)	27		
4. Education level					
No formal education/primary	30(56.6)	23(43.3)	53	1.786	0.409
Secondary	19(43.2)	25(56.8)	44		
Tertiary	11(47.8)	12(52.2)	23		
5. Working					
Yes	39(52.0)	36(48.0)	75	0.320	0.572
No	21(46.7)	24(53.3)	45		
6. Monthly Income					
No income	21 (53.8)	18(46.2)	39	3.869	0.276
≤ 2000	23(59.0)	16(41.0)	39		
2001-3500	11(37.9)	18(62.1)	29		
≥3501	5 (38.5)	8(61.5)	13		
7. Cancer Stage					
Stage 1	23(54.8)	19(45.2)	42	0.844	0.656
Stage 2	29(46.0)	34(54.0)	63		
Stage 3	8 (53.3)	7(46.7)	15		
8. Number of Chemotherapy cycle					
1st cycle	22(56.4)	17(43.6)	39	1.421	0.491
2nd cycle & 3rd cycle	21(43.8)	27(56.3)	48		
4th cycle & above	17(51.5)	16(48.5)	33		
9. Pain due to Chemotherapy					
Yes	48(49.5)	49(50.5)	97	0.054	0.817
No	12(52.2)	11(47.8)	23		
10. Worried of adverse effect due to chemotherapy					
Yes	60 (100)	60 (100)	120	0	-
11. Joined Cancer Support Society					
Yes	1 (20.0)	4 (80.0)	5	1.878	0.171
No	59 (51.3)	56 (48.7)	115		

* p <0.05

mean depression ratings were observed between the intervention and control groups at baseline (mean difference = 0.048, 95% CI = -0.345, 0.479, p = 0.749). However, at the first follow-up (M = 1.400, SD = 1.123) in the intervention group, a significant increase in mean score compared to the control group was observed in Depression. Positive significant changes were noted in the 2nd (M = 0.833, SD = 0.905) and 3rd (M = 0.617, SD = 0.993) follow-ups, with Depression scores remaining significantly higher than baseline and control group levels. In contrast, in the control group, Depression showed a significant decrease in mean score from the 1st follow-up (M = 1.883, SD = 1.151) followed by subsequent follow-ups. In Table V the results of the two-way repeated measures ANOVA analysis for depression on both groups (intervention and control) and time (baseline, until 3rd follow-up) effects and interaction between group and time showed that there were significant main effects for the group (F (1, 118) = 94.519, p < 0.001, partial $\eta 2$ = 0.158) and the interaction between group and time (F (1.997, 241.72) = 72.539, p < 0.001, partial $\eta 2$ = 0.381). Additionally, there were significant findings for time (F (2.502, 241.72) = 10.383, p <0.001, partial $\eta 2$ = 0.381). These results suggest that depression levels varied across different time points, independent of the intervention effect.

DISCUSSION

QoL

The QoL in the present study was evaluated through four domains (Physical health, Psychological, Social relationship, and Environment). A study showed that patient information on the side effects of chemotherapy treatment is essential and should be an important part of supportive care. Especially in palliative care settings, where symptom control is the main

Table II: Comparison of mean score changes in quality of life between intervention and control groups across three follow-up assessments

Outcome measures	Mean ± SD		Mean difference (95%CI)	T statistic (df)	p-value
	Intervention group (n=60)	Control group (n=6)			
Physical Health					
Baseline	63.28±14.51	65.10±15.05	1.82 (-3.53, 7.16)	0.673(118)	0.502
1st follow-up	71.92±14.81	60.98±14.78	-10.93 (-16.28, -5.59)	-4.048(118)	<0.001**
2nd follow-up	76.62± 15.02	59.60±14.79	-17.02 (-22.41, -11.63)	-6.253(118)	<0.001**
3rd follow-up	79.30± 14.63	58.33±14.38	-20.97 (-26.21, -15.72)	-7.917(118)	<0.001**
Psychological					
Baseline	59.15±12.55	56.23±15.53	-2.917 (-8.022, 2.189)	-1.13(118)	0.260
1st follow-up	60.92±15.27	52.03±17.79	-8.883 (-14.877,		
-2.890)	-2.94(118)	0.004*			
2nd follow-up	63.00±14.89	41.22±17.18	-21.783 (-27.596, -15.970)	-7.42(118)	<0.001**
3rd follow-up	65.55±18.37	36.88±15.26	-28.667 (-34.770, -22.563)	-9.30(118)	<0.001**
Social relationships					
Baseline	63.12±20.44	58.87±17.59	-4.25 (-11.14, 2.64)	-1.22(118)	0.225
1st follow-up	67.28±18.89	50.73±17.67	-16.55 (-23.16, -9.94)	-4.96(118)	<0.001**
2nd follow-up	71.77±16.74	44.10±16.56	-27.67 (-33.69, -21.65)	-9.10(118)	<0.001**
3rd follow-up	74.18±15.37	40.60±15.44	-33.58 (-39.15, -28.02)	-11.94(118)	<0.001**
Environment					
Baseline	61.37±17.40	62.33±12.14	0.97(-4.46, 6.39)	0.353(118)	0.725
1st follow-up	71.97±18.75	54.57±17.45	-17.4 (-23.95, -10.85)	-5.262(118)	<0.001**
2nd follow-up	75.15±16.54	43.77±15.40	-31.38 (-37.16, -25.60)	-10.755(118)	<0.001**
3rd follow-up	77.85±15.11	40.13±15.59	-37.72 (-43.27, -32.16)	-13.451(118)	<0.001**

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

therapeutic aim, the impact of treatment on QoL is important to be monitored as well. The present study showed that there was a significant improvement in this study's QoL in all domains (Physical health, Psychological, Social relationship, and Environment) and improved over time with repetitive counselling among patients in the intervention group. In comparison to the control group, there were significant increases in the QoL during the subsequent follow-ups. The present study showed that patients who had depression were associated with poor QoL. A randomized control study supported the present study, where continuous counselling by pharmacists improved the QoL of cancer patients undergoing chemotherapy. Another study also mentioned that the QoL and emotional well-being significantly improved among breast cancer patients who underwent group therapy intervention.[20] The study also reported that group therapy reduced the depression level among breast cancer patients, and the QoL was enhanced.[21] Adding on to that, a prospective observational single-center cohort study was conducted among early-stage breast cancer patients where depression and QoL were measured among the breast cancer patients, and a dynamic change in depression and QoL was observed when monitoring the depression level and support for breast cancer patients.[22]

Depression

In this study, there were no significant differences in depression between the intervention and control groups at baseline. These percentages include mild, moderate, and severe depression. Depression is a common comorbidity in cancer patients, with a prevalence rate ranging from 15% to 50% according to various studies.[23-25] For example, a systematic review conducted in 2017 aimed to assess the levels of depression among Iranian women diagnosed with breast cancer found that while mild depression was present, 69.4% of participants had serious levels of depression.[26]

In this current study, the intervention group that received repetitive counselling showed significant improvement in depression levels, with a decrease in mean scores over time. Compared to the control group, the intervention group exhibited substantial decreases in depression severity during subsequent follow-up assessments. Spending quality time with patients and engaging in frequent interactions were beneficial in fostering a positive attitude toward disease management. Moreover, the involvement of pharmacists presented an opportunity to impact both the patients' well-being and treatment outcomes positively. For instance, a study by Umma mentioned that chemotherapy counselling conducted by a pharmacist significantly improved the QoL and psychological outcomes of oncology patients undergoing treatment in Malaysia.[19] This underscores the critical role pharmacists play in supporting cancer patients' emotional well-being and enhancing their overall treatment experience.[19]

Another study revealed that incorporating psychosocial interventions, such as counselling, is a vital component of comprehensive cancer care.[27] These intervention help address the emotional well-being of cancer patients, improve their QoL, enhance coping strategies, and reduce the burden of depression during their cancer journey.[27] Additionally, a study by Vimala (2012) also revealed that cancer patients are invariably exposed to psychosocial stress due to the disease and the treatment strategy.[28] Implementing counselling practices can prepare cancer patients to manage depression and psycho-social challenges better.[27]

The significance of repetitive counselling by pharmacists among breast cancer patients undergoing chemotherapy

A pharmacist can be a valuable information hub for families navigating cancer treatments. Having a fundamental grasp of various chemotherapy types and the reasons behind side

Table III: Effectiveness of intervention module on quality of life between intervention and control groups over time

Source	Type III Sum of Squares	df	Mean square	F	p-value	Partial η2
Physical Health						
Group	16638.075	1	16638.075	22.952	< 0. 001**	0.163
Error (Between)	85537.792	118	724.897			
Time	1520.517	3	980.765	10.472	<0.001**	0.082
Group*Time	8922.108	1.550	5754.944	61.446	<0.001**	0.342
Error (within)	17133.875	182.940	93.658			
Psychological						
Group	35793.802	1	35793.802	58.937	<0.001**	0.333
Error (Between)	71663.696	118	607.319			
Time	1509.323	1.555	970.352	5.181	0.012*	0.042
Group*Time	18607.773	1.555	11963.041	63.878	<0.001**	0.351
Error (within)	34373.654	183.542	187.280			
Social Relationships						
Group	50491.519	1	50491.519	44.860	<0.001**	0.275
Error (Between)	132813.563	118	1125.539			
Time	909.290	1.678	541.795	10.465	<0.001**	0.081
Group*Time	15065.973	1.678	8976.971	173.392	<0.001**	0.595
Error (within)	10252.988	198.038	51.773			
Group	54869.633	1	54869.633	65.327	<0.001**	0.356
Environment						
Group	54869.633	1	54869.633	65.327	<0.001**	0.356
Error (Between)	99110.233	118	839.917			
Time	1466.817	1.872	783.493	7.174	<0.001**	0.057
Group*Time	26465.017	1.872	14136.160	129.437	<0.001**	0.523
Error (within)	24126.667	226.248	106.638			

*p < .05, **p < .001

Table IV: Comparison of mean score changes in depression between intervention and control groups across three follow-up assessments

Outcome measures	Mean ± SD		Mean difference (95%CI)	T statistic (df)	p-value
	Intervention group (n=60)	Control group (n=60)			
Baseline	1.733±1.102	1.800±1.176	0.067 (-0.345, 0.479)	0.320(118)	0.749
1st follow-up	1.400±1.123	1.883±1.151	0.483 (0.722, 0.894)	2.328(118)	0.022*
2nd follow-up	0.833±0.905	2.050±1.126	1.217 (0.8477, 1.586)	6.522(118)	<0.001**
3rd follow-up	0.617±0.993	2.400±1.304	1.783 (1.364,2.203)	8.426(118)	<0.001**

*p < .05, **p < .001

Table V: Effectiveness of intervention module on depression between intervention and control groups over time

Source	Type III Sum of Squares	df	Mean square	F	p-value	Partial η2
Group	94.519	1	94.519	22.201	<0.001**	0.158
Error (Between)	502.379	118	4.257			
Time	7.506	3	2.502	10.383	<0.001**	0.381
Group*Time	52.440	1.997	26.260	72.539	<0.001**	0.381
Error (within)	85.304	241.72	0.362			

*p < .05, **p < .001

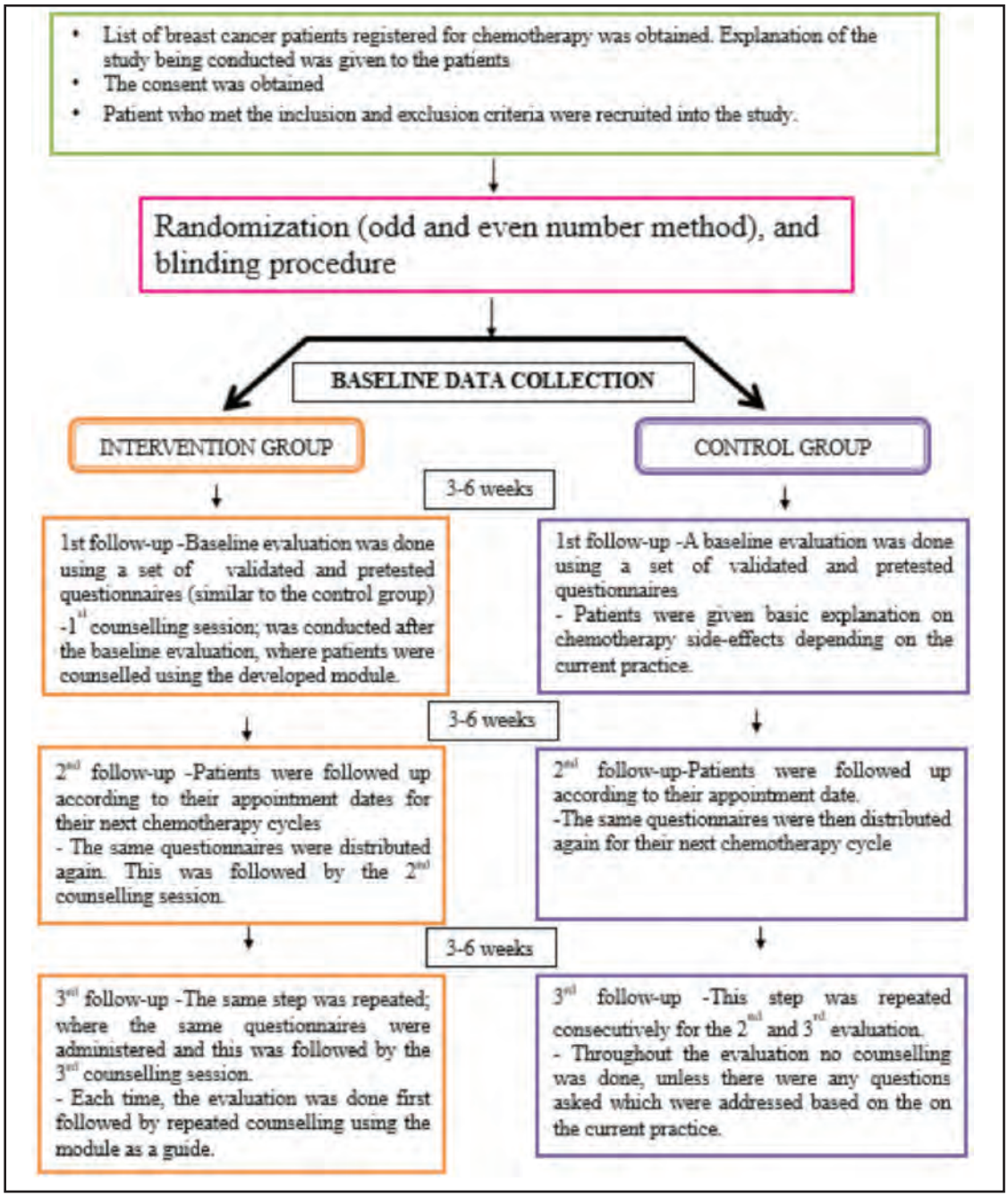

Fig. 1: CONSORT diagram of the study participants

effects is essential for effectively conveying this information to patients. Additionally, being well-versed in prevalent side effects, both in terms of pharmacological and non-pharmacological management, as well as understanding when to refer patients to physicians and the significance of support groups, are all pivotal aspects. Across numerous countries, the role of pharmacists is shifting from conventional drug-centred services to patient-centric services. This shift includes providing detailed information about chemotherapy regimens and potential side effects to individuals undergoing cancer treatment.[29] These findings align with previous research, suggesting that consistent and ongoing counselling, support, and patient care indirectly enhance mental and physical recovery.

Pharmacists play a distinct role in partnering with healthcare experts to enhance patient care. Furthermore, research has shown that continuous counselling by pharmacists improves the QoL among cancer patients undergoing chemotherapy.[20,30] The introduction of counselling sessions at the outset of systemic therapy has been associated with improved QoL outcomes. Consequently, it is recommended that pharmacists implement regular counselling sessions during cancer patients' treatment to effectively enhance their QoL both during and after the treatment period These results hold valuable implications for preserving patients' QoL throughout their cancer treatment journey.[30] Pharmacists should play a pivotal role in treating and caring for cancer patients, functioning as an integral part of the crucial

interdisciplinary oncology team. This was similarly concluded in a study where pharmacists provided continual counselling led to an enhancement in the QoL among cancer patients undergoing chemotherapy.[20] The introduction of counselling by pharmacists at the outset of systemic therapy led to improved QoL. Consequently, it is recommended that pharmacists implement counselling sessions during cancer patients' treatment to effectively enhance their QoL both during and after the treatment period.[20]

RECOMMENDATIONS

This module shows promise for hospital implementation, particularly for breast cancer patients undergoing chemotherapy. It can enhance QoL and manage depression associated with chemotherapy. The module's guidance enables pharmacists to spend quality time with each patient, addressing the psychological effects of chemotherapy and improving overall QoL. Incorporating repetitive counselling sessions at regular intervals allows for ongoing monitoring of the intervention's impact. Given the module's demonstrated effectiveness, it could be proposed to Pharmacy Practice & Development Division, Ministry of Health, Malaysia for further research and broader implementation in clinical practice. The outcomes of this study suggest avenues for further research. Future studies should use a larger sample size to better assess side effects and depression management among breast cancer patients undergoing chemotherapy. Extending the intervention duration and incorporating caregiver support could clarify its impact. Additionally, a multisite study with a more diverse population would enhance heterogeneity and reduce cross-contamination, preserving the findings' internal validity.

This study's findings can aid future researchers in identifying the specific needs of cancer patients undergoing chemotherapy. It highlights the importance for health professionals to consider factors impacting chemotherapy patients' QoL. However, a limitation is that the study only included patients from one centre, potentially limiting generalizability. Also, due to time constraints, the study only followed up on the first three chemotherapy cycles. Stage 4 cancer patients, who are often in palliative care, were excluded due to the self-administered questionnaire's nature, which could pose participation challenges. Despite these limitations, the study underscores the significance of counselling for breast cancer patients undergoing chemotherapy. The findings demonstrate the value of implementing counselling interventions to consistently monitor and enhance QoL during treatment.

CONCLUSION

The newly developed counselling module was effective in improving the QoL among breast cancer patients undergoing chemotherapy at the IKN. Notably, this study marks one of the pioneering efforts in Malaysia, as it evaluates the effectiveness of repetitive chemotherapy counselling conducted by pharmacists among breast cancer patients. The outcomes of this study hold significant value and relevance for breast cancer patients, as they present a way to uphold QoL throughout the chemotherapy treatment. Due to that, it is suggested to propose repetitive counselling sessions by pharmacists during the treatment of cancer patients, with the objective of enhancing their QoL both during and after the chemotherapy treatment.

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A cross-sectional study on the second victim experience and support at Sarawak General Hospital: A tertiary public hospital in Borneo Island, Malaysia

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ABSTRACT

Introduction: Second victim experience (SVE) refers to the emotional and psychological impact experienced by healthcare providers who are involved in patient safety incidents (PSIs). Despite growing awareness of patient safety in healthcare organizations, remedial actions often focus only on the first victim, the patient. Therefore, it is important to recognize and address the emotional and physical toll that PSIs to ensure the well-being of and to promote a culture of safety in healthcare settings. Hence, this study was initiated to determine the prevalence of SVE, assess symptoms related to SVE and evaluate the level of support needed by healthcare providers.

Materials and Methods: The Second Victim Experience and Support Tool for Recovery (SVEST-R) questionnaire was utilized to conduct an anonymous survey on the healthcare providers in Sarawak General Hospital (SGH) from August to October 2018.

Results: A total of 482 respondents participated in the survey and 46.1% of the respondents reported SVE following their involvement in PSIs. Notably, symptoms such as flashbacks, fear, and stress tend to persist for longer durations compared to other symptoms. It is worth noting that non-work-related support received the highest mean (medical doctors = 3.83; nurses = 3.70), indicating that respondents preferred to seek emotional support from their friends and families. Furthermore, nurses reported a significantly higher experience of absenteeism following PSIs than doctors (p=0.003). In addition, most respondents expressed a desire for discussion or counselling with a respected peer or supervisor following their involvement in PSIs.

Conclusion: Present study reported a relatively high prevalence of SVE among healthcare providers at SGH. Hence, proactive measures, including non-work related and supervisor support, are essential in facilitating their overall well-being and successful recovery.

KEYWORDS:
Patient safety incident, second victim, second victim experience, second victim phenomenon, support resource

INTRODUCTION

Fast-paced healthcare environments and complex systems often give rise to medical errors that can harm patients or, in severe cases, lead to fatalities.[1] Unintended or unexpected patient outcomes, commonly referred to as patient safety incidents (PSIs), are unavoidable in healthcare settings and may result in adverse outcomes not directly attributable to the patient's underlying condition.[2] Near misses, which are incidents that do not result in harm, are also considered PSIs. According to Reason's Swiss Cheese Model, PSIs are typically systemic rather than isolated events.[3] Patients directly affected by PSIs are termed "first victims," while healthcare providers experiencing emotional distress from such events are considered "second victims," and healthcare organizations suffering reputational and operational consequences are identified as "third victims".[4]

Despite growing recognition of patient safety within healthcare organizations, interventions often focus solely on protecting patients while neglecting the profound impact on healthcare providers.[5] Second Victim Experience (SVE), a concept first described by Wu in 2000 [6], highlights the emotional and physical toll on healthcare providers involved in PSIs.[6] These individuals may experience diminished confidence, stress, and burnout, which can impair their professional performance.[7,8] Although research has broadened the understanding of SVE, studies reveal that over two-thirds of healthcare providers experience it during their careers, yet fewer than a third receive institutional support.[9,10] Addressing the needs of these providers is crucial to fostering resilience, ensuring their well-being, and promoting a culture of safety.

Globally, prompt emotional support and structured debriefing techniques have shown promise in mitigating the impact of SVE.[11,12] In Malaysia, limited data exist on the

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prevalence and symptoms of SVE, particularly in tertiary public hospitals. Sarawak General Hospital (SGH), a major tertiary hospital in Kuching, Malaysia, presents a unique setting to explore this issue due to its diverse patient population and resource constraints. Previous studies have identified gaps in SGH's patient safety culture, emphasizing the need for enhanced resources and training.[13] This study aims to determine the prevalence of SVE, assess its symptoms, and evaluate support needs among healthcare providers using the validated Second Victim Experience and Support Tool for Recovery (SVEST-R).[14] Findings will provide critical insights into improving patient safety and healthcare quality in Malaysia, advocating for targeted interventions, policies, and research to support affected healthcare providers and ultimately enhance patient care outcomes.

MATERIALS AND METHODS

Study design & study participants

A cross-sectional study via a paper-based, self-administered questionnaire was conducted in SGH with approximately 4,568 staff and 995 beds, from August to October 2018. Convenience sampling was employed due to challenges to openly recruiting healthcare providers who have encountered PSIs, as there are perceptions that PSIs reflect a lack of competency and hinder open discussion about such experiences.[15] In addition, this exploratory study invited only medical doctors or nurses providing direct patient care in SGH. Sample size was calculated using an overall probability of the prevalence of second victims (p = 0.5), probability of the first type error (alpha = 0.05) and the precision (d = 0.05). Hence, the required sample size was 384.[16]

Study instrument

The distributed questionnaire comprised three sections namely, (1) sociodemographic characteristics which include profession, gender, age, ethnicity, education level and occupational tenure; (2) SVEST-R; and (3) the desired forms of support by the second victim. The SVEST-R is a validated instrument that consists of 29 items and seven dimensions to measure SVE and support received. The seven dimensions assess the desirability of different forms of support needed which includes psychological distress, physical distress, colleagues' support, supervisors' support, organizations' support, non-work-related support, and professional self-efficacy. Additionally, there are two outcomes measured by the instrument, namely turnover intentions and absenteeism. Participants were to respond using a 5-point Likert scale ranging from 1 (strongly do not desire) to 5 (strongly desire). Burlison et al. state that the higher a score is for a specific dimension, the greater it indicates in terms of the level of psychological distress, physical distress, a decreased level of self-efficacy, and a perceived lack of support.[17] In addition, the desired forms of support were rated using the 5-point Likert scale, where the desired options are 5 (strongly desired) or 4 (desired), 3 (neutral) represents the neutral option, and the not desired options are 2 (not desired) or 1 (strongly not desired).

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 22.0. Standard descriptive statistics were used to summarize the demographic data by using counts with percentages for categorical variables and means with standard deviations (SD) for the scores from SVEST-R were regarded as the outcome variables. The p value was determined by one-sample independent t-tests. All calculated p values < 0.05 were considered statistically significant.

Ethical consideration

This study was registered with National Medical Research Register (NMRR) with registration number NMRR-18-1953-43147 and ethical approval from Medical Research and Ethics Committee (MREC) was obtained prior to the recruitment of study subject/participant.

RESULTS

Demographic characteristics

The survey had a total of 482 respondents, surpassing the minimum requirement of 384 to account for non-response. Majority of the respondents were in the age group of 26 to 30 years (n=169, 35.1%), while 82% of the respondents were nurses (n=395) (Table I). The respondents in this study represented a diverse range of ethnic backgrounds, including Chinese, Malay, Indian, Iban, Bidayuh, and others. The largest ethnic group was Malay, accounting for 31.7% of the total respondents (n=153). Additionally, the highest education attainment of the respondents varied, spanning from diplomas to Doctor of Philosophy (PhD) degrees, encompassing specialty trainings such as post-basic and sub-specialty certifications. The majority of respondents (47.3%) held a diploma, which is the minimum qualification required for nurses in Malaysia. The occupational tenure of the respondents also varied, ranging from less than one year to over twenty years; with the majority of respondents having an occupational tenure of one to five years (n=152, 31.5%).

Symptoms and duration of second victim experience

The symptoms and duration of second victim experience varies among respondents. Present finding shows the 19 most commonly associated symptoms with SVE and their corresponding duration which can vary from as short as 24 hours to over a year (Figure 1). These symptoms encompass a spectrum of severity, ranging from mild manifestations like feelings of shame to more severe effects such as burnout or leaving their profession. Notably, symptoms such as hypervigilant, flashbacks, fear, and stress tend to persist for longer durations compared to other symptoms. Present findings corroborated with the study by Vanhaect et al. where the most common symptoms that bothered second victims were hypervigilance, flashbacks, and fear.18 In addition, 40 to 50% of the respondents had experienced more severe symptoms such as intention to leave a discipline or profession, wanting to move to another organisation or even fear of losing their job. The impact of these symptoms may be influenced by the severity of PSIs, which could explain the variability in durations observed.[19]

Prevalence of SVE and degree of harm in the PSI

Present finding shows that the prevalence of SVE among medical doctors and nurses was 46.1% (n=222) (Table II) which corroborated with study conducted by Mayo Clinic,

Table I: Socio-demographic characteristics of respondents

Items	n=482 (%)
Profession	
Doctor	87 (18)
Nurse	395 (82)
Gender	
Male	76 (15.8)
Female	406 (84.2)
Age range	
20-25	27 (5.6)
26-30	169 (35.1)
31-35	100 (20.7)
36-40	67 (13.9)
41-45	63 (13.1)
46-50	27 (5.6)
51 and older	29 (6)
Ethnicity	
Malay	153 (31.7)
Chinese	78 (16.2)
Indian	20 (4.1)
Iban	98 (20.3)
Bidayuh	102 (21.2)
Othersa	31 (6.4)
Education level	
Diploma	228 (47.3)
Diploma with post-basic qualifications	132 (27.4)
Degree	97 (20.1)
Master	21 (4.4)
Master (with sub-specialty)	2 (0.4)
PhD	2 (0.4)
Occupational tenure (year)	
< 1	9 (1.9)
1-5	152 (31.5)
6-10	125 (25.9)
11-15	65 (13.5)
16-20	64 (13.3)
20 and above	67 (13.9)

[a]Others include the minority ethnic groups such as Kenyah, Lun Bawang and Kelabit.

Table II: Prevalence of SVE and degree of harm in the PSIs

Prevalence of SVE and degree of harm	Doctors n	Nurses n	Total n (%)
Ever felt like a second victim after PSI			
No	46	214	260 (53.9)
Yes	41	181	222 (46.1)
Degree of harm in the PSIa			
No harm	22	138	160 (72.1)
Temporary harm	13	37	50 (22.5)
Permanent harm	2	2	4 (1.8)
Fatal harm/Death	4	4	8 (3.6)

[a]Degree of harm in the PSI among respondents who answered "Yes"

United States where the prevalence was reported at 47.8%.[18] In addition, other studies found that healthcare providers are likely to experience PSIs at least once in their careers with varying percentages, ranging from 10.4% to 30%.[20–22]

Domain descriptive findings from SVEST-R

Present survey findings reported a higher mean score for psychological distress (medical doctors = 3.35; nurses = 3.22) than physical distress (Table III). Psychosomatic symptoms such as sleep disturbances and appetite change are physical symptoms that are caused or exacerbated by psychological factors. Physical distress may arise because of the toll that the SVE takes on the individual's overall health and resilience.

Desired forms of support by the second victim

Second victim support opinions desirability by respondents is presented using the 7 survey items in Table IV. Findings from Table IV shows that 53.5% of the respondents desired to discuss the event with their manager or supervisor, and only 15.6% did not desire this option (mean = 3.46, SD =1.06).

Table III: SVEST dimensions and outcome variables

SVEST Measuresa	Doctor (n=87)			Nurse (n=395)		P-value[b]
	No.of items	n (%) for mean score ≥ 4	Group mean (SD)	n (%) for mean score ≥ 4	Group mean (SD)	
Dimensionc						
1) Psychological distress	4	30 (34.5)	3.35 (0.90)	116 (29.4)	3.22 (0.87)	0.225
2) Physical distress	4	23 (26.4)	3.01 (0.98)	107 (27.1)	3.06 (0.88)	0.666
3) Colleague support	4	23 (26.4)	3.44 (0.65)	134 (33.9)	3.53 (0.67)	0.253
4) Suçervisor support	4	21 (24.1)	3.47 (0.49)	87 (22.0)	3.38 (0.61)	0.159
5) Institutional support	3	21 (24.1)	3.23 (0.71)	117 (29.6)	3.37 (0.66)	0.073
6) Non-work-related support	2	58 (66.7)	3.83 (0.76)	264 (66.8)	3.70 (0.77)	0.171
7) Professional self-efficacy	4	15 (17.2)	3.13 (0.64)	84 (21.3)	3.10 (0.73)	0.694
Outcomed						
8) Turn-over intention	2	22 (25.3)	3.09 (0.89)	94 (23.8)	2.96 (0.89)	0.229
9) Absenteeism	2	11 (12.6)	2.59 (0.96)	89 (22.5)	2.92 (0.89)	0.003

[a]The respondent's score for each dimension or outcome was defined as the mean of 2–4 items each rated on a 5-point scale of 1 = strongly disagree and 5 = strongly agree.
[b]P-value is determined by one-sample independent t-tests.
[c]A higher score for each specific dimension represents experiencing more psychological distress, more physical distress, decreased professional self-efficacy, and a greater degree to which support is perceived as inadequate.
dA higher score for each specific outcome represents more turnover intention and absenteeism.
Abbreviations: SD, standard deviation; SVEST, Second Victim Experience and Support Tool.

Table IV: Second victim support opinions desirability by respondents

Survey Item	Desire		Not desire		Neutral		Mean	SD
	n	(%)	n	(%)	n	(%)		
1) The ability to immediately take away from my unit for a little while	162	(33.6)	161	(33.4)	159	(33.0)	2.94	1.18
2) A specified peaceful location that is available to recover and recompose after one of these types of events	196	(40.7)	121	(25.1)	165	(34.2)	3.15	1.12
3) A respected peer to discuss the details of what happened	242	(50.2)	87	(18.0)	153	(31.7)	3.37	1.02
4) An employee assistance program that can provide free counselling to employees outside of work	225	(46.7)	97	(20.1)	160	(33.2)	3.30	1.12
5) A discussion with my manager or supervisor about the event	258	(53.5)	75	(15.6)	149	(30.9)	3.46	1.06
6) The opportunity to schedule a time with a counsellor at my hospital to discuss the event	217	(45.0)	107	(22.2)	158	(32.8)	3.23	1.12
7) A confidential way to get in touch with someone 24 hours a day to discuss how my experience may be affecting me	222	(46.1)	107	(22.2)	153	(31.7)	3.26	1.16

Abbreviations: SD, standard deviation

DISCUSSION

Prevalence of SVE and degree of harm in the PSI

Present findings depict a significantly higher proportion of nurses who experienced SVE compared to doctors which could be attributed to the fact that nurses typically spend more time at the bedside, providing direct care and interacting closely with patients. Nurses close proximity with the patients makes them more likely to witness adverse events or errors first-hand, thus intensify feelings of guilt, self-doubt, and responsibility.[20–22] Furthermore, it is worth noting that nursing is a predominantly female profession, while the medical field is relatively gender-balanced in Malaysia. Gender disparity between the medical doctors and nurses could contribute to differences in SVE as female nurses may experience more emotional distress, guilt, and self-blame after adverse events.

Findings from this survey also shows that 72.1% (n=160) of the respondents were involved in PSI without any harm to patients because healthcare providers need adhere to ethical principles and have a duty to provide safe and effective care. However, when PSIs occurs, healthcare providers may question whether they could have prevented the incident or if their actions were in line with their professional obligations. Regardless of patient harm, moral distress and ethical uncertainties can contribute to the SVE.

There was a higher proportion of respondents (3.6%) who admitted they had been involved in fatal PSIs as compared to PSIs resulting in permanent harm (1.8%). Fatal harm or death PSIs could have a potentially detrimental effect on the second victim such that having an ingrained memory of a past event in question can make a healthcare providers inculcate a tendency to minimise it in the future, which

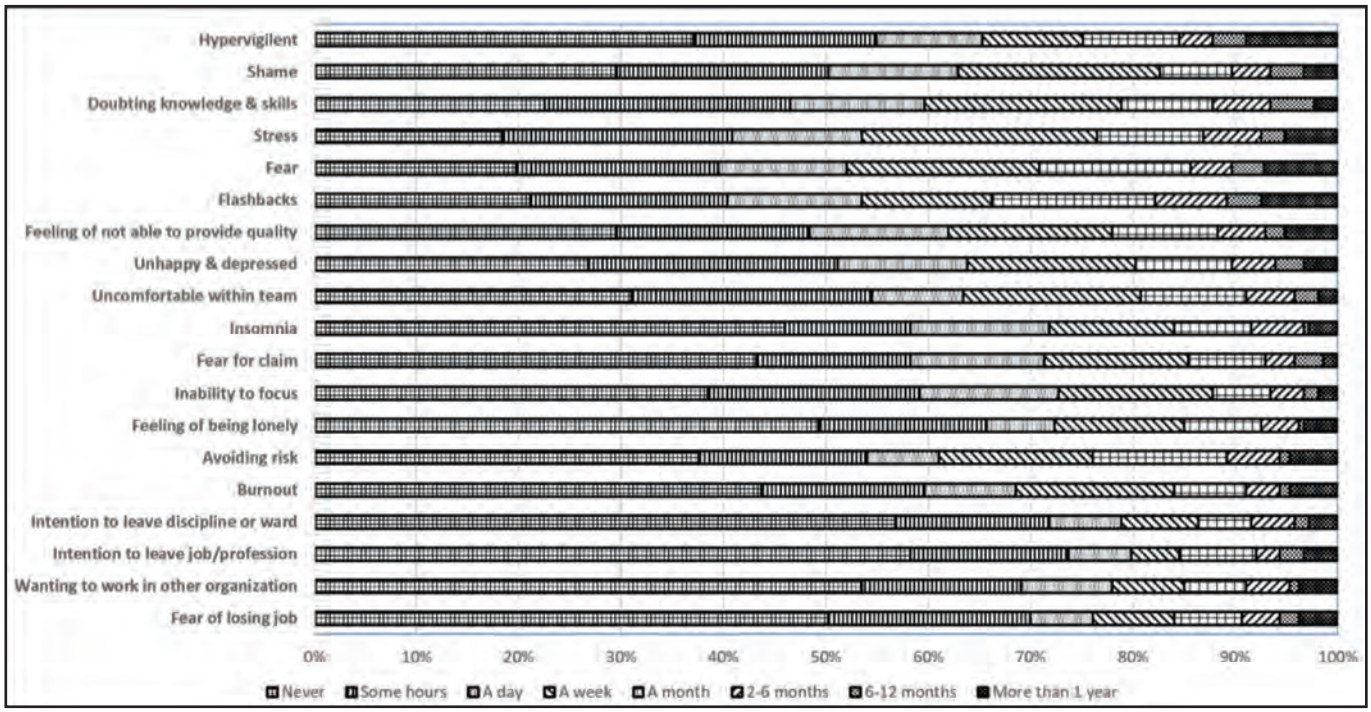

Fig. 1: Symptoms and durations of second victim experience in the aftermath of a patient safety incident
(Note: Results were based on 222 respondents (of the 482 respondents) who answered the question about whether they felt like a second victim after a patient safety incident)

might invariably affect decision-making.[23,24] Healthcare providers may even refuse to accept similar patients because of that inculcated fear, which can be considered as "negative defensive medicine".[25]

Domain descriptive findings from SVEST-R

Interestingly, respondents' professional self-efficacy was not significantly affected by the occurrence of PSIs to the same extent as psychological and physical distress. Present finding highlights the importance of identifying which stressor category might have a severe impact on respondents' professional self-efficacy in the event of a medical error, and of taking appropriate measures to minimise the impact of these stressors and focus on addressing psychological and physical distress rather than professional self-efficacy. Therefore, it is essential that all healthcare providers are equipped with high resilience, the capacity to manage with stress and stressors within an environment and the ability to interact in a way to promote personal well-being.[26]

In addition, findings reported in Table III shows that non-work-related support received the highest mean (medical doctors = 3.83; nurses = 3.70), indicating that respondents preferred to seek emotional support from friends and families. Whereas the mean for colleague support (medical doctors = 3.44; nurses = 3.53), supervisor support (medical doctors = 3.47; nurses = 3.38), and institutional support (medical doctors = 3.23; nurses = 3.37) received lower mean scores. Only 24.1% of medical doctors and 29.6% of nurses expressed a desire for support that could be offered by the hospital. Therefore, the SVEST-R tool is important in evaluating the quality of support resources for improvement within the organisation and offering site-specific preferred support options.

Second victim tend to have an intention to turn-over and be absent from work if support is perceived as inadequate and SVE occurs.[27] Present findings show that a greater proportion of respondents (25.3% of medical doctors and 23.8% of nurses) reported having turn-over intentions, while 12.6% of medical doctors and 22.5% of nurses reported the possibility of being absent from work as a result of SVE. Healthcare providers who experienced being a second victim often feel as though they let down the patient and often question their career path. In addition, healthcare providers that experienced SVE have even decided to leave their chosen profession, and tragically, a few have resorted to suicide as a means to escape their anguish. To alleviate the suffering and facilitate the recovery of second victims, it is vital for healthcare organisations to establish organised support systems, especially for PSI with severe or fatal outcomes.[28]

However, there were no significant statistical differences between medical doctors and nurses for all dimensions and outcomes, except for absenteeism. Nurses reported a significantly higher experience of absenteeism following PSIs than medical doctors (p=0.003). This is consistent with the finding from this study in which nurses experienced a higher degree of SVE than doctors. Nurses may be more susceptible to absenteeism associated with SVE because of proximity to patients and greater emotional attachment. As a result, they may feel a greater sense of personal responsibility for adverse events or patient outcomes, leading to increased emotional distress. Such emotional distress experienced by nurses may contribute to increased absenteeism.[29]

Desired forms of support by the second victim

Present findings corroborated with a study by Burlison et al.[29] such that the most desired second victim support option was

"a respected peer to discuss the details of what happened." Gathering input from healthcare providers on their desired forms of support can furnish tailored guidance for augmenting provisions for individuals who have experienced SVE. Moreover, healthcare providers who interact with respected peers or supervisors feel valued and cared for, which assists them in moving forward.[29]

Meanwhile, the least desirable option of support is item 1 which is ('the ability to immediately take away from my unit for a little while') with 33.6% of respondents desired, and 33.4% of respondents did not desire this support item (mean = 2.94, SD =1.18). The mean for other support items was higher than the neutral score of 3. Senior management and intermediate managers must be committed to building a non-punitive culture in response to errors, thereby encouraging reporting and learning from errors to prevent recurrence.[30]

Coping strategies and recommendations

The emotional impact of a PSI and the appropriate coping strategies to mitigate it have a dynamic relationship which can evolve according to varying circumstances. A mistake can elicit a specific emotional response, which may prompt a second victim to choose a particular coping strategy that can, in turn, elicit another response. Therefore, it is crucial to select appropriate coping strategies to overcome the impact of SVE, as dysfunctional coping strategies can adversely affect health worker well-being, reduce self-confidence, and increase fear of making mistakes, hence potentially leading to increased risk for future PSIs.[31,32] Literature reveals two main coping strategies: the problem-focused strategy and the emotion-focused strategy. These are crucial for second victims to develop an effective coping strategy by dealing with the error, analysing it, and learning from it, either alone or in collaboration with colleagues.[33,34]

Debriefing sessions have been identified as beneficial for assisting second victims to cope with the emotional impact and demands of their daily workload. Debriefing is a discourse that focuses on sharing and analysing information after an incident occurred. It may follow a simulated or actual experience and provides learners with a forum to reflect on and learn from their mistakes.[35] The process of debriefing can be initiated promptly following a PSI. Debriefing sessions may involve the participation of a skilled facilitator. However, it is also possible for teams to conduct self-debriefing exercises with the aid of debriefing scripts and cognitive aids.[36] During debriefing sessions, second victims could analyse the PSIs that happened and evaluate their actions and clinical decision-making.

A supportive and non-punitive culture within the healthcare setting is recommended to help mitigate the severity of SVE.[37,38] Such culture fosters learning and continuous improvement, as well as reducing the burden of blame and self-doubt on second victims. In addition, leadership plays a crucial role in creating and sustaining these cultures. Leaders should demonstrate a commitment to patient safety, learning, and the well-being of healthcare providers by promoting a blame-free environment, encouraging open communication, and recognizing the importance of psychological support. Leaders who prioritise the well-being of their staff contribute to a culture where second victims feel supported, valued, and empowered to engage in error prevention and recovery processes.

Peer responders can assist and facilitate the second victims to effective psychological first aid, according to the experience of a group at Johns Hopkins.[39] The peer responders are professional colleagues who, in most cases, are the first to give the second victims the support they need, and hence these peer responders should ideally be trained in psychological first aid. In addition, it is important for experienced and senior healthcare providers to render appropriate guidance to the junior healthcare providers when discharging their services to provide optimal patient care.

Limitations

First, the causal effect relationship could not be established due to the nature of a cross-sectional study. Second, convenience sampling can be liable to selection bias because it does not offer representativeness. Third, it is also possible that the response rate of this self-administered questionnaire would be negatively impacted by potential respondents' fear of admitting that something went wrong, and of the possible repercussions, since blame culture is not uncommon in Malaysia. Lastly, we did not conduct a multivariate analysis since this study is mostly exploratory and is intended to generate hypotheses. This study serves a basis for further research in Malaysia, hence both clinical significance and statistical significance shall not be within the remit of our study.

CONCLUSIONS

This study demonstrated a relatively high prevalence of SVE among healthcare providers in a tertiary public hospital in Borneo Island. Furthermore, present findings highlight the importance of implementing proactive measures to support second victims and underscores the significance of non-work related support, as well as supervisor support. These endeavours play a vital role in safeguarding the well-being and sustained effectiveness of healthcare providers, ultimately benefiting both individuals and the quality of care provided to patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Quantitative characterisation of carotid atherosclerotic plaque neovascularisation using contrast-enhanced ultrasound imaging: A feasibility study

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ABSTRACT

Introduction: Contrast-enhanced ultrasound (CEUS), an in vivo imaging tool for evaluating intraplaque neovascularisation (IPN), is an increasingly researched marker of susceptible atherosclerotic plaque. This study aims to assess the feasibility of quantifying carotid IPN using CEUS and to identify and characterise the neovascularisation in carotid plaques. The hospital's ethical committee approved the study, and the informed individual consent form of CEUS was obtained from all patients before the examination.

Materials and Methods: Seventy-one patients with carotid atherosclerotic plaques (95 plaques) were studied on CEUS. Contrast enhancement in the plaque was evaluated with visual interpretation and quantitative analysis. The intraplaque neovascularisation (IPN) test was graded on a 3-point scale. IPN was quantified using dedicated software for CEUS image analysis.

Results: It was found that the CEUS quantitative parameters were significantly different for plaques with varying types of echoes. The quantitative parameters also differed in soft, hard, and mixed plaques. The quantification of carotid IPN using CEUS was found feasible. The quantitative parameters measured from CEUS provide multiple references for carotid IPN of different echo types. This can help identify and monitor unstable atherosclerotic plaques.

Conclusion: CEUS has the potential to be an important tool in clinical application, specifically for diagnosing carotid atherosclerotic plaque features and vulnerability.

KEYWORDS:
Arteriosclerosis, Atherosclerotic plaques, Contrast-enhanced ultrasound, Contrast sensitivity, Neovascularisation

INTRODUCTION

Atherosclerosis is characterised by the constriction of arteries due to lipid and calcium-forming plaques that impede the normal flow of oxygenated blood and increase the risk of cardiovascular events such as myocardial infarction, stroke, and transient ischemic attack.[1] The latest report shows that about 270 million people in China currently have carotid atherosclerosis, and 200 million have carotid artery plaques.[2] Neovascularisation, the growth of microvascular networks within plaques, plays a critical role in plaque vulnerability and increases the risk of rupture, leading to adverse cerebrovascular events.[3] It has been established that plaque vulnerability and intraplaque neovascularisation (IPN) are related to the progression of atherosclerotic disease. Neovascularisation is the emergence of functional microvascular networks perfused by red blood cells. The body promotes the growth of blood vessels to supply the tissue that forms within an arterial wall, plaques, by providing a place for these tissues to grow. Recent advances in contrast-enhanced ultrasonography (CEUS) have demonstrated that ultrasound contrast agents allow for visualising these small microvasculature networks with a slow flow.[1]

Invasive and non-invasive testing techniques are the primary categories of carotid plaque examination techniques. Ultrasound, magnetic resonance imaging (MRI), computed tomography angiography (CTA), digital subtraction angiography (DSA), and other techniques are used to assess carotid plaque. DSA is the "gold standard," but it is invasive, expensive, and uses ionising radiation. It also cannot evaluate the wall and plaque interior.[4] CTA offers more intuitive images through three-dimensional reconstruction technology and is more sensitive to intra-plaque calcification. However, apart from its inability to detect neovascularisation in plaque, it also uses ionising radiation and there is a possibility of allergic reactions in patients due to the use of contrast material. Whereas MRI takes a long scanning time, as well as significantly impacted by motion and breathing artifacts. High-resolution magnetic resonance imaging (HRMRI) is time-consuming, expensive, not conducive to follow-up, and not suitable for some patients with non-MRI compatible metal implants. Carotid artery ultrasonography is currently the most commonly used clinical method to identify carotid plaques. CEUS uses microbubble contrast agents to reveal blood flow and neovascularisation in plaques. Fleiner et al.[5] found a more significant occurrence of new capillaries in the plaques of symptomatic individuals by comparing 22 patients

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displaying clinical symptoms with 27 patients having asymptomatic carotid atherosclerotic plaques. Contrast agents are restricted to the microvasculature and can enter the microvasculature network. Therefore, the appearance of microbubbles within the plaque is a manifestation of local neovascularisation. CEUS allows real-time, non-invasive observation of blood flow in plaques using sulphur hexafluoride microbubbles.

A study performed by Sedding et al.[6] highlighted the connection between neovascularisation in the plaque and the risk of haemorrhage and inflammation, both of which are major contributors to ischaemic stroke. Vulnerable plaque, known as unstable plaque, is strongly associated with ischemic stroke and transient ischemic attack (TIA).[7] Intraplaque neovascularisation (IPN), characterised by weak, immature vessels, is a marker of plaque instability and increases the likelihood of rupture and bleeding.[8] Routine ultrasound examination of the carotid artery can detect the thickness of arterial intima-media and the existence and size of the plaque. However, it cannot show the new blood vessels in the plaque well, and the density of new blood vessels in the plaque is closely related to the stability of the plaque. Contrast-enhanced ultrasound (CEUS) as intravascular tracers can display neovascularisation in plaques, making up for the shortcomings of conventional ultrasound examinations. CEUS is a new technique for evaluating neovascularisation in carotid plaques. Compared to traditional ultrasound diagnosis, CEUS technology significantly increases resolution sensitivity and specificity by enhancing dispersed echoes with contrast agents.[9-10] CEUS can display micro-vessels and blood perfusion in real time, reflect the blood perfusion of the neovascular through the degree of contrast enhancement in carotid atherosclerotic plaque, and identify the density of neovascular enhancement in plaques. This study mainly aims to analyse the neovascularisation in carotid plaques with different types of echoes quantitatively based on current technology, CEUS.

MATERIALS AND METHODS

Participant Recruitment

A total of 71 patients with carotid atherosclerotic plaques (95 plaques) who were diagnosed and treated in Yichang Second People's Hospital, Hubei, China, from May 2022 to May 2023, were selected as the study subjects. They comprised 42 males and 29 females; their ages ranged from 47 to 81 years, with a mean of 62.24±8.73 years. Subjects were selected based on the following inclusion and exclusion criteria.

The inclusion criteria are: 1) Carotid atherosclerotic plaque formation with a thickness ≥ 1.2mm was found by ultrasonography; 2) Those aged ≥30 years old. The decision to include patients 30 years old and above only was based on several key considerations. Firstly, there are low prevalence of carotid atherosclerotic plaque in young adults. Secondly, it is based on the institutional patient demographics in which our hospital, a specialized geriatric and chest pain centre, primarily serves an older patient population. As such, the majority of patients presenting to our institution for vascular evaluation are typically older than 30 years of age. Thirdly, we aimed to investigate the clinical implications of carotid plaque neovascularization in a group at higher risk for cardiovascular events, such as stroke and myocardial infarction. While it is acknowledged that early-onset atherosclerosis can occur, it is relatively rare and often associated with specific risk factors, such as familial hypercholestrolaemia or systemic inflammatory diseases. Given the low prevalence and distinct clinical presentation of early-onset disease, it was determined that the inclusion of younger patients would not significantly contribute to the primary objectives of this study.

Whereas the exclusion criteria are 1) Those who had cerebrovascular diseases in the past three months; 2) Those with complete occlusion of the common carotid artery or occlusion of the internal carotid artery; 3) Those with cardiac, pulmonary, and renal insufficiency. Cardiac insufficiency is defined as an ejection fraction (EF) of the left ventricle of less than 50%. Renal insufficiency is defined as elevated blood creatinine, elevated cystatin C, and decreased glomerular filtration rate on laboratory tests; Pulmonary insufficiency is defined as a ratio of first-second expiratory volume on exertion of less than 50 percent of the predicted value on pulmonary function testing; 4) Those who are allergic to ultrasound contrast agents; 5) Those with psychiatric disorders who are unable to complete the study; 6) Those who are pregnant or breastfeeding; 7) Those who have carotid plaque calcifications involving greater than 30% of plaque area. This study obtained approval from the Research Ethics Committee of Yichang Second People's Hospital, Hubei, China. All subjects were informed of the inspection process and signed the informed individual consent forms for the contrast-enhanced ultrasound before the examination.

Conventional US Imaging

An Aplio 500 ultrasound system, as shown in Figure 1 (Toshiba, Canon Medical Systems Corporation, Tokyo, Japan), was used with a high-frequency probe (frequency at 4 - 11MHz), and the mechanical index was set at 0.08, the frame frequency was 12 frames/second, the depth was around 3 - 5cm. During the examination, the individual was examined by lying in a supine position with the head turned 45 degrees to the contralateral side. The American Society of Echocardiography's consensus scanning procedure was used to acquire images.[11] The patient was positioned supine to evaluate both left and right carotid arteries, scanning from the common carotid artery through the carotid bifurcations with a focus on the internal and external carotid arteries on both sides using two-dimensional ultrasound.

Each anatomical region was assessed from a variety of angles. The gain and imaging depth were modified individually for each patient to achieve optimal ultrasound images. Plaques were thoroughly checked for presence on both sides. Three images with clear echoes of plaques from both the cross-sectional and longitudinal sections were selected to record the plaque's size, shape, position, echo, and edge, and the images were saved to the system. After the two-dimensional images of the plaque were displayed, the probe was fixed on the plaque for local amplification, and the carotid intima-media thickness (IMT) and the length of the carotid artery plaque were measured. The target plaque was counted three times, and the average of three measurements

was taken and recorded in the system as a primary measurement before CEUS.

CEUS Imaging

The CEUS imaging was performed using the same ultrasound system mentioned in the previous section. The carotid plaque CEUS examinations were performed by two diagnostic ultrasonographers who had each been trained in both ultrasound diagnosis work for more than ten years and CEUS for more than five years. They jointly confirmed the outcomes and reached a consensus on judgments. The diagnostic ultrasonographers were blinded to the history of all subjects, and they kept the subjects' information strictly confidential. Two Aplio 500 ultrasound systems of the same configuration were used for this study.

A freeze-dried powder contrast agent, SonoVue (Bracco Suisse SA, Milan, Italy), was employed, as shown in Figure 2A. Each bottle contains 59 mg of SF6 (sulfur hexafluoride) gas and 25 mg of freeze-dried powder. The contrast agent powder and 5 ml of normal saline were mixed into a suspension liquid, as shown in Figure 2B. Then, 2.4 ml of the suspension was aspirated and pushed into the patient's body through the cubital vein in 2 - 3 seconds using an 18-gauge intravenous cannula. Then, 5 ml of normal saline was injected to flush the injection channel. The contrast effect was observed within the carotid artery lumen 15 to 30 seconds following injection, allowing for the capture and preservation of high-quality contrast images for approximately 1 minute post-administration.

The area of interest was continuously imaged for approximately 90 seconds using the dual-screen contrast mode of two-dimensional ultrasound and CEUS. The images were saved for further analysis, as illustrated in Figure 3, and stored digitally in DICOM (Digital Imaging and Communications in Medicine) format for later offline examination. The quantitative analysis software, specifically the Time Curve Analysis (TCA) function equipped with the ultrasound instrument, was used to generate a time-intensity curve (TIC); if multiple regions of interest were observed in the same patient, the interval between the second CEUS should be at least 15 minutes. Subjects were monitored for 30 minutes before they were allowed to leave in case any complications developed.

Observation Indicators

According to the contrast distribution in the plaque, the semiquantitative visual grading standard for intraplaque neovascularisation is based on the following rules[12]: Grade I: no enhancement, no microbubble contrast agent in the plaque; Grade II: a minor enhancement, a small amount of microbubble contrast agent in the plaque, see punctate, little flake-like enhancement; Grade III: massive enhancement, a large amount of microbubble contrast agent can be seen in the plaque.

Plaques were characterised by their appearance on standard ultrasound images. They were classified according to widely used criteria as follows[13]: (a) Soft plaques with echogenicity lower than that of the surrounding adventitia for over 80% of the plaque area, without acoustic shadowing; (b) Hard plaques with echogenicity equal to or greater than that of the surrounding adventitia for over 80% of the plaque area, without acoustic shadowing; (c) Calcified plaques containing over 90% circumferential calcification and displaying as bright echoes within the plaque along with acoustic shadowing; (d) Mixed plaques containing less than 90% circumferential calcification or having associated echo-dense and anechoic regions occupying less than 80% of the plaque area.[13] In this study, we enrolled subjects with soft, hard, and mixed plaques. Because calcified plagues with calcifications involving greater than 30% of plaque area are excluded as they are challenging to analyse by the time-intensity curve (TIC) quantitative assessment.

Then, for quantitative assessment, firstly, a stable continuous dynamic image was chosen. Next, the region of interest (ROI) was selected, with one ROI being placed in the plaque as the evaluation ROI and the other in the lumen as the corresponding match between the two. The plaque's border was traced following its shape to prevent other areas from being covered. A rectangular sampling frame placed in the middle of the carotid lumen where the plaque was located would be the reference area (intraluminal). Then, the time-intensity curve (TIC) was computed and produced by the software.

The main quantitative analysis parameters of TIC were the peak intensity (PI), baseline intensity (BI), enhancement intensity in the arterial lumen, and time to peak is the time from the start of intravenous injection of contrast agent to the time when the maximum intensity is reached in the region of interest (TTP), mean transit time (MTT), plaque enhancement intensity (EI) = PI - BI, Ratio value = EI/enhancement intensity in the arterial lumen. The EI parameter measures the SonoVue intravascular tracer's intensity variations between pre- and post-injections within the plaque ROI.

Statistical Analysis

In this study, data analysis was performed using SPSS 22.0 statistical software (IBM, USA). The normality of measurement data was tested using the Shapiro-Wilk method, and normally distributed data were expressed as mean ± standard deviation. Group comparisons were conducted using analysis of variance (ANOVA), and pairwise comparisons between groups were performed using the LSD method. Categorical data were presented as counts (percentages) and analysed using the chi-square test or Fisher's exact test. A two-tailed test was used, and differences were considered statistically significant at $p<0.05$.

RESULTS

A single carotid ultrasound and CEUS examination typically take around 30 minutes. The images of carotid plaque acquired through conventional ultrasound are depicted in Figure 3, while those obtained using CEUS are presented in Figure 4.

Among 71 patients with carotid atherosclerosis, 95 plaques were identified as more than 1.2 mm thick, including 46 soft plaques, 37 mixed plaques, and 12 hard plaques. The enhancement rates (Enhancement rate = (grade II + grade III)/total number of cases × 100%) of plaques with different echo types were as follows: soft plaque contrast-enhancement

Table I: Semiquantitative visual grading standard for different plaque types and the enhancement rates

Groups	Numbers	Grade I	Grade II	Grade III	Enhancement rate	χ^2	p-value
Soft plaques	46	2	16	28	95.7%*	13.291	<0.001
Mixed plaques	37	5	18	14	86.5%*		
Hard plaques	12	6	5	1	50.0%		

Note: Compared with the Hard plaques group, *p<0.05

Table II: Comparison of EI values for different plaque types

Plaque types	Soft plaque (n=46)	Hard plaque (n=12)	Mixed plaque (n=37)	F-value	p-value
EI value (dB)	11.95±3.33*	5.47±1.36*	7.76±2.21*	38.540	<0.001
P (compared with soft plaque)		<0.001	<0.001		
P (compared with hard plaque)			0.013		

*Values are stated as mean ± standard deviation

Table III: Comparison of Ratio values for different plaque types

Plaque types	Soft plaque (n=46)	Hard plaque (n=12)	Mixed plaque (n=37)	F-value	p-value
Ratio value	0.53±0.18*	0.27±0.09*	0.32±0.11*	26.241	<0.001
P (compared with soft plaque)		<0.001	<0.001		
P (compared with hard plaque)			0.320		

*Values are stated as mean ± standard deviation

Table IV: Comparison of TTP values for different plaque types

Plaque types	Soft plaque (n=46)	Hard plaque (n=12)	Mixed plaque (n=37)	F-value	p-value
TTP（s）	18.28±1.98*	26.79±2.11*	9.44±1.69*	453.039	<0.001
P (compared with soft plaque)		<0.001	<0.001		
P (compared with hard plaque)			<0.001		

*Values are stated as mean ± standard deviation

Table V: Comparison of MTT values for different plaque types

Plaque types	Soft plaque (n=46)	Hard plaque (n=12)	Mixed plaque (n=37)	F-value	p-value
MTT（s）	7.65±1.43*	28.03±2.03*	22.81±3.02*	659.229	<0.001
P (compared with soft plaque)		<0.001	<0.001		
P (compared with hard plaque)			<0.001		

*Values are stated as mean ± standard deviation

accounted for 95.7%, mainly manifested as grade II enhancement and grade III enhancement, followed by mixed plaques (86.5%); hard plaques accounted for the least amount (50.0%), mainly showing grade I enhancement and grade II enhancement, as shown in Table I. Fisher's exact probability method was used, and the difference in enhancement rates between the three groups was statistically significant, with the Hard plaques group having a significantly lower enhancement rate than the other two groups (p<0.05).

Based on CEUS images, the quantitative parameter values of CEUS images were found to be different in soft, hard, and mixed plaques. The EI and Ratio values of soft plaques were significantly higher than those of hard plaques and mixed plaques (p<0.05); the TTP and MTT of hard plaques were significantly higher than those of soft plaques and mixed plaques (p<0.05), the TTP of soft plaques was significantly higher than that of mixed plaques (p<0.05), the MTT of soft plaques was significantly lower than that of mixed plaques (p<0.05) as shown in Table II – V.

DISCUSSION

SonoVue has been demonstrated to be safe, as it does not become trapped in small blood vessel networks and does not spread across vascular or micro-vessel walls. There is no evidence of any adverse effects associated with SonoVue.[14] In a 49,100 case study analysing the safety of adverse events with SonoVue, it was noted that SonoVue had a favourable safety profile, with a low incidence of adverse events, most of which were mild and of short onset and duration.[15] In another study conducted on 502 children, Sonovue contrast was found to be safe, feasible, diagnostically reliable, and

Fig. 1: Canon Aplio 500 ultrasound system

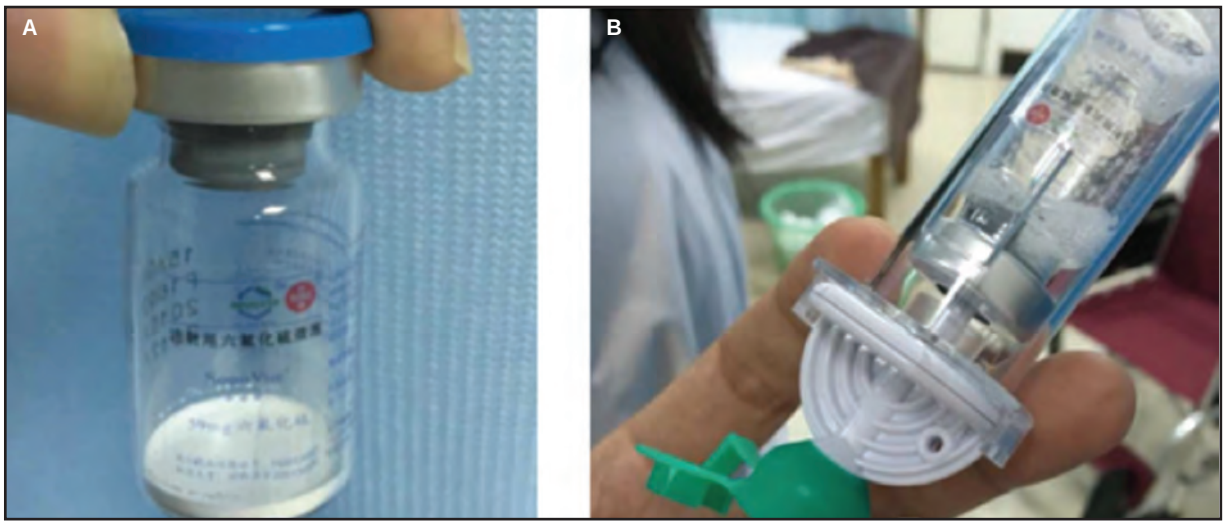

Fig. 2: Contrast agent SonoVue.
(A) Freeze-dried powder is a form of contrast agent stored in a bottle. (B) The contrast agent powder is mixed with normal saline.

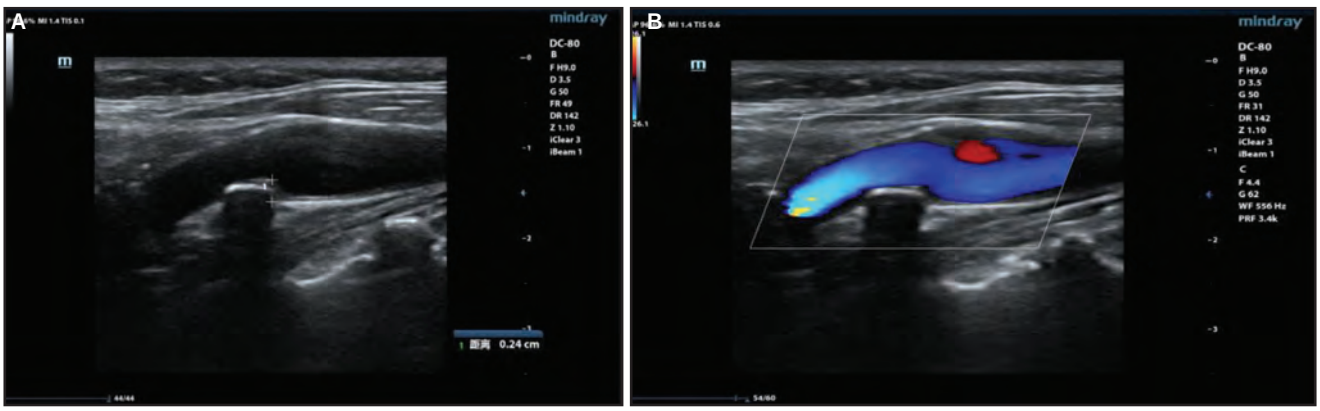

Fig. 3: Conventional ultrasound of carotid mixed plaque.
(A) Two-dimensional ultrasound image of a mixed echogenic plaque in the longitudinal section of the internal carotid artery. (B) Colour Doppler image of the same mixed echogenic plaque in the longitudinal section of the internal carotid artery.

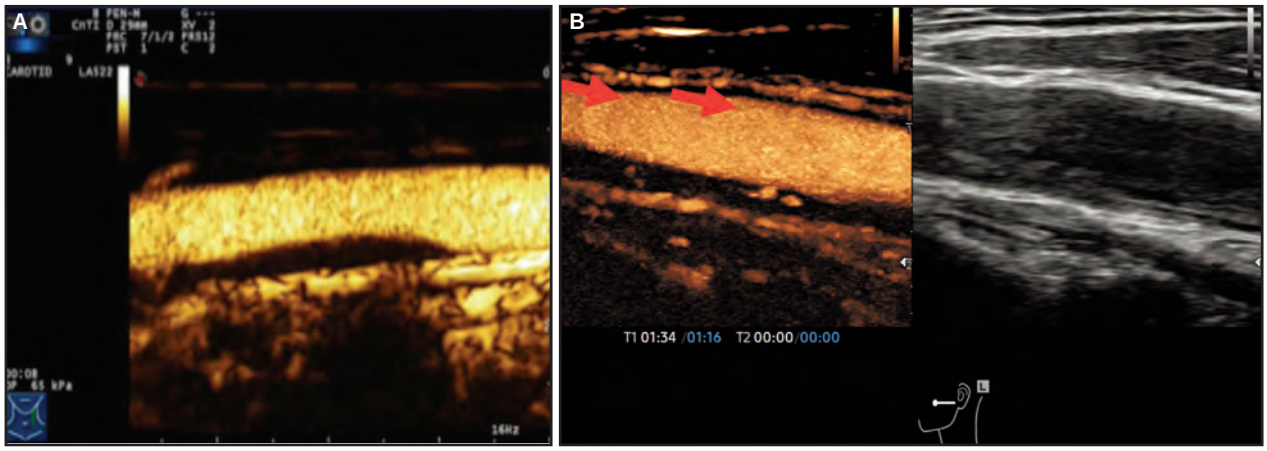

Fig. 4: Contrast-enhanced ultrasonography of carotid soft plaque.
(A) Longitudinal image of the common carotid artery shows an unobvious contrast agent in the soft plaque using the contrast mode. (B) A large amount of contrast agent (Red arrow) is seen inside the plaque of the longitudinal image of the common carotid artery using the dual-screen contrast mode of two-dimensional ultrasound and CEUS.

effective.[16] Sulphur hexafluoride gas is mainly excreted from the body via respiration through the pulmonary circulation within 15 minutes of injection. In CEUS imaging, microbubbles exhibit a nonlinear response to ultrasound insonification due to their high compressibility and resonance, distinguishing them from tissue's linear response. This distinct behaviour allows for differentiation between tissue and microbubble responses.

Soft plaques are also called unstable plaques, prone to rupture, thrombosis, and myocardial infarction. Hard plaques are also called stable plaques, which are more durable than soft plaques and less prone to local rupture and thrombus formation. Mixed plaques are plaques that have the characteristics of soft plaques and hard plaques, presenting mixed echoes. Among the 95 plaques identified in our study, it was found that there were 46 soft plaques, 12 hard plaques, and 37 mixed plaques, indicating that there were relatively more unstable plaques in patients with carotid atherosclerosis. The distribution of CEUS enhancement grading of carotid plaques of different echo types showed that the lower the plaque echo, the more obvious the CEUS enhancement was, and the proportion of contrast enhancement in soft plaques was the highest, accounting for 95.7%, with grade II and III enhancement as the major part; mixed plaques were the second, with a contrast enhancement of 86.5%, and hard plaques accounted for the lowest proportion of enhancement, accounting for 50.0%, with grade I and II as the major part. The difference in the distribution of CEUS enhancement grades of carotid plaques of different echo types was statistically significant ($p<0.05$).

This also shows that soft and mixed plaques are more likely to be enhanced by CEUS, while hard plaques are less likely to be enhanced. This is because the interior of soft plaques is mainly composed of lipids and cholesterol, while the interior of hard plaques is mainly composed of calcification. Lipid necrosis can enhance inflammatory activity within atherosclerotic plaques, thereby inducing the formation of new blood vessels. Soft and mixed plaques have more blood vessels than hard plaques, which greatly increases the vulnerability of plaques. Therefore, such plaques need further examination to clarify their stability. Accurately assessing the nature of plaques can better guide the dosage of drugs, this is of great clinical value.

The results of preclinical studies have shown that there is a direct relationship between plaque enhancement and neovascularisation,[17] which has also been confirmed in clinical practice. Giannoni et al. (2009) found that plaque intraplaque enhancement was associated with an increase in small immature micro-vessels (20 – 30 mm diameter).[18] The ultrasonic contrast agent caused a rise in the intra-plaque signal intensity. In our study, the enhanced intensity of CEUS for soft, mixed and hard plaques was (11.95±3.33) dB, (7.76±2.21) dB, and (5.47±1.36) dB, respectively. The enhanced intensity ratios were 0.53±0.18, 0.32±0.11, and 0.27±0.09, respectively. The EI and Ratio values of soft plaques were significantly higher than those of hard plaques and mixed plaques ($p<0.05$). The distribution of CEUS enhancement quantitative parameters of carotid plaques of different echo types also showed that the lower the plaque echo, the more obvious the CEUS enhancement was. This result showed a correlation between visual grading of intraplaque enhancement and quantitative analysis of computed enhancement intensity based on CEUS. Plaques with high CEUS visual grading showed increased EI and ratio values, as displayed in the Tables. These findings are consistent with previous research results.[17]

Additionally, our findings indicate that soft plaques exhibit more pronounced contrast enhancement than other plaques. This aligns with the results of prior studies.19 Among the cohort of patients with soft plaques, a more significant proportion exhibited contrast enhancement upon visual interpretation and more pronounced enhancement as evaluated through EI and ratio value analysis. This discovery implies that CEUS has the potential to detect highly vascularised and vulnerable soft carotid plaques.

CEUS shows that the formation of neovascularisation in carotid plaques has a good correlation with the results of histological examination, and it is best to use quantitative software to analyse and evaluate. However, its role in daily clinical practice still needs further confirmation.[4] The TIC can be used to quantitatively analyse the neovascularisation inside the carotid plaque, effectively avoiding the measurement bias caused by subjective factors in the semiquantitative visual grading.[20] CEUS quantitative parameters can reflect the pathological characteristics of atherosclerotic plaques. PI can reflect the density of new blood vessels in the plaque, and the higher the PI, the greater the density of new blood vessels.[21] TTP mainly reflects the perfusion pattern of neovascularisation in the plaque, in which the more minor the TTP, the faster the perfusion rate.[22]

Clinical studies have shown that increased intra-plaque neovascularisation is an independent risk factor for the progression of atherosclerosis and an essential feature of vulnerable plaques.[8] Therefore, the larger the PI, the smaller the TTP, and the higher the plaque vulnerability. In our study, the EI value and Ratio value of soft plaque were significantly higher than those of hard plaque and mixed plaque ($p<0.05$), the TTP of hard plaques were significantly higher than those of soft plaques and mixed plaques ($p<0.05$), these results are highly consistent with previous studies above.

Our results also confirm that soft plaques are the most vulnerable plaques, which means the TIC curve can efficiently and accurately identify and characterise unstable carotid plaques. Based on CEUS imaging quantitative parameters, a more reliable reference value for clinical diagnosis of the nature of carotid atherosclerotic plaques and plaque vulnerability is offered. Our study has certain limitations, primarily due to its single-centre design. As the hospital where the study was conducted is a geriatric facility with specialised stroke and chest pain centres, most patients are those with underlying conditions such as diabetes, coronary heart disease or hypertension. This may introduce a degree of selection bias in our findings. Therefore, our results may differ from those of large-scale multicentre studies from other academic institutes. Our research is still clinically significant, and further in-depth investigations will be conducted.

CONCLUSIONS

Based on the safety of Sonovue as well as the reasonable scan time of 30 minutes, it was found that performing CEUS imaging of carotid IPN at our hospital is feasible when carotid plaque stability needs to be assessed for clinical benefits. CEUS imaging allowed better identification and quantification of carotid IPN through quantitative parameters, specifically EI, Ratio Values, TTP, and MTT. Quantitative CEUS parameters can provide additional information on plaque vulnerability based on semi-quantitative visual assessment, which can help in patient screening and appropriate interventions. CEUS can quantitatively evaluate the intensity of neovascularisation inside plaques of different echo types and thus provide a reference for clinical diagnosis of the nature of carotid atherosclerotic plaques and plaque vulnerability.

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DISCLOSURE STATEMENT

The authors report there are no competing interests to declare.

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ORIGINAL ARTICLE

Prevalence and risk factors of myocardial injury in patients with COVID-19: A retrospective study

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ABSTRACT

Introduction: The coronavirus disease of 2019 (COVID-19) predominantly impacts the pulmonary system; however, it also has harmful consequences for the cardiovascular system through the occurrence of myocardial injury.

Materials and Methods: This retrospective study analysed 119 COVID-19 patients admitted to Al-Sultan Abdullah Hospital (HASA) from March until December 2020. Demographics, medical histories, admission laboratory results, electrocardiogram (ECG), echocardiogram (echo), were captured from the hospitals' health records. Myocardial injury is an injury to the myocardium that can be diagnosed by elevated cardiac troponin T or I level above the 99th percentile upper reference limit (URL), an abnormal ECG, and an abnormal echo. Data were analysed using Statistical Package for Social Sciences (SPSS) Version 27.

Results: From this study, it was founded that the prevalence of myocardial injury is 36.1% (43 subjects out of 119). The risk factors are older age (odds ratio, 2.347; p=0.028), males (odds ratio, 2.019; p=0.125), Indians (odds ratio, 3.659; p=0.296), hypertension (odds ratio, 2.776; p=0.009), diabetes mellitus (odds ratio, 1.732; p=0.155) and category 4 and 5 COVID-19 patients (odds ratio, 2.325; p=0.038).

Conclusion: Myocardial injury is prevalent among patients affected by COVID-19 and is associated with older age, hypertension and category 4 and 5 COVID-19. The researchers suggested conducting a more thorough investigation of the sizable population in multiple settings and conducting a prospective study where all infected COVID-19 patients have to undergo several tests, such as ECG, troponin T, and echocardiogram.

KEYWORDS:
Prevalence, myocardial injury, COVID-19, risk factor.

INTRODUCTION

COVID-19 is a disease that is spread by the novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China.[1] It is becoming a pandemic and causing an effect on the whole world. SARS-CoV-2 is categorised as a beta coronavirus, characterised by its huge size, spherical shape, enveloped structure, and non-segmented positive-sense single-stranded RNA genome, which spans around 30 kilobases.[1] Despite being largely a respiratory illness, observational studies have demonstrated a close relationship between COVID-19 and cardiovascular disease.[2] This then triggers the activation of immunological mechanisms, including T-cells and B-cells, which create antibodies, mediators, and cytokines, leading to myocardial inflammation.[2]

Numerous published studies have indicated a correlation between higher fatality rates in COVID-19 infections and myocardial injury among patients with COVID-19. 28% of patients inflicted with COVID-19 signs of myocardial injury and elevated troponin levels in the blood.[3] Additionally, the mortality rates of patients with cardiac damage evidence were higher than those of those without (51.2% vs. 4.55%, p<.001).[5] The study also found that acute renal failure, electrolyte abnormalities, and acute respiratory distress syndrome (ARDS) were complications that frequently occurred in heart injury patients, indicating that the involvement of the heart negatively impacts these patients' prognosis.[3]

Those who have cardiovascular comorbidity and exhibit high-risk variables, such as being male, advanced age, diabetes, hypertension, or obesity, are susceptible to experiencing cardiac injury and are considered part of the vulnerable group in relation to COVID-19.[4] It is clear that myocardial injury is a common complication in COVID-19 patients in the severe and critical intensive care units, and that advanced age, arterial hypertension, immunomodulator use, and a high Sequential Organ Failure Assessment score are independent predictors of COVID-19 occurrence and severity.[5] Cardiovascular problems are also common in these patients, and they are associated with a greater mortality rate.[5]

After conducting research, the researcher found limited published articles about COVID-19-related myocardial injury in Malaysia. The issue of insufficient concentration within a relevant field has been acknowledged and tackled in Malaysia. The researcher intends to conduct this study within the specific context of Malaysia in order to investigate and find risk factors that are linked to the prevalence of myocardial injury among individuals who have received a positive diagnosis for COVID-19.

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MATERIALS AND METHODS

Study Design and Population

This is a retrospective study that uses solely accessible secondary data. The participants must undergo one of the following examinations while hospitalised: electrocardiogram (ECG), echocardiography (echo), or troponin T. Except for those with suspected symptoms of myocardial injury, these procedures (ECG, echo, and troponin T) are not routinely performed on all COVID-19 patients admitted to Al-Sultan Abdullah Hospital (HASA). These three studies serve as markers for the diagnosis of myocardial injury in COVID-19 patients. The population of the study are 119 patients with positive COVID-19 all categories, Malaysian, age above 12 years old, and both genders.

Research Instrument

The data collection form which consists of five different sections (Demographics, medical histories, admission laboratory results, ECG, and echo) was used as an instrument to collect data from the Al-Sultan Abdullah Hospital (HASA) medical records department.

Sample collection

The UiTM Research Ethics Committee (Ref. number: REC/11/2021 (MR/881)) and the Director of HASA (Ref. number: 500-HUiTM (PT.8/3/1)) have approved this study. The data has been collected at the HASA medical record department. All the data patients with COVID-19 were screened and collected from hardcopy records or database files using the computer in the medical record department. Positive COVID-19 cases were screening from October 2021 until February 2022. All ECG, echo and troponin T results were interpreted and reviewed by a cardiologist who is one of research team members.

Definition

Myocardial injury is defined as injury in the myocardial and can be detected by elevated cardiac troponin T or troponin I greater than the 99th percentile upper reference limit (URL).[6] In the context of COVID-19, myocardial injury, defined by an elevated troponin level, is caused primarily by non-ischaemic myocardial processes such as severe respiratory infection with hypoxia, sepsis, systemic inflammation, pulmonary thrombosis and embolism, cardiac adrenergic hyperstimulation during cytokine storm syndrome, and myocarditis.[7] Any injury to the myocardium can be diagnosed based on increased troponins T or troponin I, electrocardiographic changes in ST segments, and echocardiographic wall motion abnormalities or wall thickening.[8] This must be correlated with the COVID-19 symptoms, clinical features, and investigations (ECG, cardiac biomarkers (troponin) and echo). Investigation results were analysed to fit the clinical diagnosis of myocarditis and ruling out other possibilities of elevated troponin.

Statistical Analysis

All respondents' socio-demographic information, medical and health history, were analysed using Statistical Packages for Social Sciences (SPSS) Version 27. Descriptives statistics were used to calculate the prevalence rate. A crosstab test was used to identify the odd ratio contributing to developing myocardial injury among patients with COVID-19 in HASA.

Demographic characteristics of subjects

A total of 119 patients were included from October 2021 until February 2022 at HASA. Table I displays the demographics, clinical characteristics, and laboratory characteristics based on the presence of myocardial injury. Patients with myocardial injury were 81.4% male, with a mean age of 59 years old. COVID-19 patients with myocardial injuries were associated with older age (P=0.028). Most of the myocardial injuries had occurred in those aged over 61 years (27.9 %). Meanwhile, 20.9% of myocardial injuries had occurred in patients aged over 71 until 80 years of age. The predominant racial group in our dataset was Malay, comprising 79% and not being equally distributed among race groups because Malay is the largest race in Malaysia.

Prevalence of myocardial injury in patients with COVID-19

The majority of the myocardial injury had occurred in those in COVID-19 categories 4 (44.2%) and 5 (27.9%). A total of 43 patients (36.1%) had abnormal ECG, abnormal echo and laboratory-confirmed troponin T positivity for myocardial injury during the hospitalisation. The result showed that 3 in 10 patients with COVID-19 might develop myocardial injury (Table I).

Risk factors of myocardial injury in patients with COVID-19

To determine the risk factors for myocardial injury in patients with COVID-19, a crosstab analysis of myocardial injury among COVID-19 patients with clinical data was performed (Table I). The result showed that older age (odds ratio, 2.347; p=0.028), male (odds ratio, 2.019; P=0.125), Indian (odds ratio, 3.659; P=0.296), hypertension (odds ratio, 2.776; p=0.009), diabetes mellitus (odds ratio, 1.732; P=0.155) and category 4 and 5 COVID-19 patients (odds ratio, 2.325; p=0.038) are risk factors associated with the incidence of myocardial injury. Older age, hypertension and category 4 and 5 COVID-19 patients are significant with occurrence of myocardial injury among patients with COVID-19. Due to the small sample size, there is no significant correlation between Indians and the occurrence of cardiac injury.

Electrocardiogram (ECG), Echocardiogram (echo) and Troponin T Characteristics of Patients COVID-19

The ECG was tested in 57 patients (47.8%), and 24 (42.2%) were abnormal. 14 (58.3%) sinus tachycardia, 1 (0.04%) sinus bradycardia, 1 (0.04%) atrial flutter, 2 (0.08%) atrial fibrillation, 2 (0.08%) ST elevation, and 4 (0.16%) ST depression (Table II). 22 (18.48%) did echo, and 19 (86.36%) was abnormal, while 24 (20.16%) underwent testing for high-sensitivity troponin T level, and 12 (50%) were raised (>14 ng/L). 13 did ECG and echo, 6 (46.1%) had abnormal ECG and echo, 1 (7.7%) had sinus tachycardia with abnormal echo, 2 (15.4%) had sinus bradycardia with abnormal echo, and 3 (23%) had ST depression with abnormal echo. 21 did the ECG and troponin T test; abnormal ECG and troponin T were 7 (33.33%) ST depression and 2 (28.5%) raised in troponin T, sinus tachycardia and 3 (42.8%) raised in troponin T and atrial fibrillation and 2 (28.5%) raised in troponin T. 5 did echo and troponin T; 3 (60%) had abnormal echo and were raised in troponin T. 3 did ECG, echo, and troponin T; 3 (100%) had abnormal ECG, echo, and were raised in troponin T.

Table I: Demographic data of patients with COVID-19 (n=119)

Characteristics	Myocardial injury				
	All (n=119)	With (n=43)	Without (n=76)	p-value (²)	Odds ratio
Demographic					
Age (years old)					
Younger					
12 - 20	1 (0.8%)	0 (0%)	1 (1.3%)	0.028	0.426
21 - 30	21 (17.6%)	3 (7%)	18 (23.7%)		
31 - 40	10 (8.4%)	3 (7%)	7 (9.2%)		
41 - 50	16 (13.4%)	7 (16.3%)	9 (11.8%)		
51 - 60	23 (19.3%)	7 (16.3%)	16 (21.2%)		
Older					
61 - 70	28 (23.5%)	12 (27.9%)	16 (21.1%)		
71 - 80	14 (11.8%)	9 (20.9%)	5 (6.6%)		2.347
81 - 90	6 (5%)	2 (4.7%)	4 (5.3%)		
Gender					
Male	87 (73.1%)	35 (81.4%)	52 (68.4%)	0.125	2.019
Female	32 (26.9%)	8 (18.6%)	24 (31.6%)		0.495
Race					
Malay	95 (79.8%)	34 (79%)	61 (80.3%)	0.876	-
Chinese	21 (17.6%)	7 (16.3%)	14 (19.2%)	0.768	-
Indian	3 (2.5%)	2 (4.7%)	1 (0.5%)	0.296*	-
Comorbid					
Hypertension	53 (44.5%)	26 (60.5%)	1 (2.3%)	0.009	2.776
Diabetes Mellitus	48 (40.3%)	21 (48.8%)	27 (22.7%)	0.155	1.732
Hyperlipidemia	36 (30.3%)	13 (30.2%)	27 (35.5%)	0.997	-
Asthma	8 (6.8%)	2 (4.7%)	23 (30.3%)	0.709*	-
Cancer	6 (5%)	1 (2.3%)	6 (8%)	-	-
Chronic obstructive	1 (0.8%)	1 (2.3%)	5 (6.6%)	-	-
pulmonary disease (COPD)	9 (7.6%)	5 (11.6%)	0 (0%)	-	-
Ischemic heart disease (IHD)	3 (2.5%)	1 (2.3%)	4 (5.3%)	-	-
Chronic kidney disease (CKD)	1 (0.8%)	1 (2.3%)	2 (2.6%)	-	-
Transient ischemic attack (TIA)	1 (0.8%)	1 (2.3%)	0 (0%)	-	-
Acute kidney injury (AKI)	1 (0.8%)	1 (2.3%)	0 (0%)	-	-
COVID-19 categories					
Mild - Moderate					
Category 1	8 (6.7%)	2 (4.7%)	6 (7.9%)	0.038	0.430
Category 2	31 (26.1%)	6 (14%)	25 (32.9%)		
Category 3	9 (7.6%)	4 (9.3%)	5 (6.6%)		
Severe and critically ill					
Category 4	49 (41.2%)	19 (44.2%)	30 (39.5%)		2.325
Category 5	22 (18.5%)	12 (27.9%)	10 (13.2%)		
Point prevalence of myocardial injury	43/119 x 100 = 36.1 % 3:10 patients with COVID-19 develop MI				

*Fishers exact test

DISCUSSION

In this study, the prevalence of myocardial injury was 36.1% (43 out of 119), indicating that 3 out of every 10 COVID-19 patients developed myocardial injury. A study conducted in China, Germany, and the United States similarly found that myocardial damage is common in COVID-19 patients. [9-12] These studies covered 42 to 985 participants and reported a prevalence of myocardial damage ranging from 28.9% to 46%.[9-12]

Older patients, males, Indians, hypertension, diabetes mellitus, and COVID-19 categories 4 and 5 are all risk factors for myocardial injury. Consistent with prior studies,[13,14] the myocardial injury patients in our study were older. Similar to these observations, the researchers also found that patients with cardiac injury tended to be older.[15,16] Elderly patients were considered "frail" due to increased comorbidities, low cognitive condition, diminished resistance to shocks, and impaired compensatory abilities.[17] Elderly people are more prone to cardiac injury due to vascular ageing, myocardial remodelling, and immunological senescence.[18,19]

The study also discovered that COVID-19 patients with myocardial injury were more likely to be men. This finding was reinforced by a prior study, which indicated that male COVID-19 patients are at a higher risk of developing myocardial injury.[13,20-23] Previous research discovered that the clearance function of inhaled particles in small airway sections decreased with age.[24] Upper airway size decreases with age, which is especially noticeable in males.[25] Furthermore, aged males have fewer immune cells and an inverted CD4/ CD8 T-cell ratio than females, resulting in reduced immune surveillance and clearance.[26] However, the study from Italy found different results.[27] Their study showed that myocardial injury could be associated with female patients.[27]

This study was conducted in Malaysia, which has a multiracial population, including Malay, Chinese, and Indian. According to the study, Indian patients with COVID-19 are at a higher risk of developing myocardial injury. A study conducted in the United States discovered that the majority racial group in their sample was white, accounting

Table II: Electrocardiogram, Echocardiogram and Troponin T characteristics of patients with COVID-19

Test	Finding Myocardial Injury (n=43)
ECG	n = 57
Normal	33 (57.8%)
Abnormal;	24 (42.2%)
Sinus Tachycardia	14 (58.3%)
Sinus Bradycardia	1 (0.04%)
Atrial Flutter	1 (0.04%)
Atrial Fibrillation	2 (0.08%)
ST Elevation	2 (0.08%)
ST Depression	4 (0.16%)
Echo	n = 22
Normal	3 (13.6%)
Abnormal	19 (86.4%)
Troponin T	n = 24
Normal	12 (50%)
Raised	12 (50%)
ECG and ECHO	n = 13
Normal	
Abnormal;	
Sinus Tachycardia	1 (7.7%)
Sinus Bradycardia	2 (15.4%)
ST Depression	3 (23%)
ECG and Troponin T	n = 21
Normal	14 (66.7%)
Abnormal;	7 (33.3%)
Sinus Tachycardia and raised troponin T	3 (42.8%)
Atrial Fibrillation and raised troponin T	2 (28.5%)
ST Depression and raised troponin T	2 (28.5%)
Echo and Troponin T	n = 5
Normal Echo and no raised in troponin T	2 (40%)
Abnormal Echo and raised in troponin T	3 (60%)
ECG, Echo and Troponin T	n = 3
Abnormal ECG, Echo and raised in troponin T	3 (100%)
ST Depression	2
Sinus Tachycardia	1
Abnormal Echo	3
Raised in Troponin T	3

for 79.5% and equally dispersed throughout both categories.[28] The findings suggest that non-Hispanics were more likely than Hispanics to have myocardial damage (20.1% vs. 12.4%).[28] Another study conducted in the United States discovered that an African American patient with COVID-19 had a 43% prevalence of cardiac injury, which was higher than previously published findings.[29] Patients with elevated troponin levels showed a sixfold greater risk of death compared to those without.[29]

Furthermore, this study discovered a history of comorbidities (hypertension and diabetes mellitus) are high risk to get myocardial injury among patients infected with COVID-19. The previous research also found that hypertension and diabetes mellitus are high-risk factors for myocardial injury.[22,27,30-32] In this study, patients have comorbidities but no previous history of myocardial injury. Patients infected with COVID-19 may have myocardial injury due to the wide-ranging effects of cardiac inflammation, which appears to be the primary feature of the infection.[33]

The researchers found that COVID-19 categories 4 (severe) and 5 (critically ill) are high risk to get myocardial injury. Pneumonia that requires extra oxygen and a catastrophic illness involving several organ failures are the main causes of cardiac injury in COVID-19 categories 4 and 5.34 Various studies have revealed that categories 4 and 5 patients infected with COVID-19 are more likely to get myocardial injury. A mendelian randomisation research on COVID-19 discovered that severe respiratory symptoms and hospitalisation may increase the risk of myocardial injury.35 Furthermore, myocardial injury and cardiovascular issues were common in patients hospitalised to the intensive care unit with severe and critical COVID-19, and both were related to higher mortality.[5] A systematic study discovered that myocardial injury appears to be associated with severe COVID-19 illnesses, particularly in hospitalised patients, who should be constantly watched and treated.[36]

Limitations and recommendations for future studies

This study has some limitations, which the authors have noted. As with much other research in this field, this one was retrospective, and the selection of participants for cardiac troponin testing will have introduced a significant bias. This study is a retrospective study, where the researchers only used the available secondary data from October 2021 until February 2022. Recommendation for future researchers could be included more sample size and conduct a prospective study where all infected COVID-19 patients have to do several testings' such as ECG, troponin T and echocardiogram

test. This prospective study could provide conclusive finding regarding the incidence of myocardial injury among infected COVID-19 patients. Apart from study design, the sample size and study duration also have to improve in future study. Due to the small size, the researchers recommended doing an in-depth study of the population and setting for a conclusive finding.

CONCLUSION

Research findings revealed that myocardial injury is prevalent in patients affected by COVID-19 and is associated with older age, hypertension and category 4 and 5 COVID-19. This study is concurrent with a previous study where the incidence of myocardial injury occurred among elderly, comorbid and category 4 and 5 COVID-19. A prospective study with a large sample size is needed for future studies.

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ETHICS APPROVAL AND INFORMED CONSENT

The UiTM Research Ethics Committee (Ref. number: REC/11/2021 (MR/881)) and the Director of UiTM Hospital (Ref. number: 500-HUiTM (PT.8/3/1)) approved this study.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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Exploring musculoskeletal disorders in end-stage kidney disease: A systematic review

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ABSTRACT

Introduction: This study focuses on the association between musculoskeletal disorders and chronic kidney disease (CKD), specifically end-stage kidney disease (ESKD). Its primary objective is to explore the spectrum of musculoskeletal disorders and to identify their prevalence rates and symptoms within diverse CKD subpopulations.

Materials and Methods: The screening process yielded 13 studies conducted in various countries and regions. These studies, employing designs such as cross-sectional, cohort, and clinical trials, focused on CKD patients across different stages, including early and late-stage CKD.

Results: The study revealed that musculoskeletal disorders are a considerable concern within the CKD population but are insufficiently explored among ESKD patients. Common musculoskeletal disorders identified include osteoarthritis, osteoporosis, fibromyalgia, carpopedal spasm, and chronic musculoskeletal pain syndrome. The prevalence of these disorders varied, with sub-group analysis revealing higher prevalence among hemodialysis patients compared to pre- and non-dialysis patients. While musculoskeletal pain remains consistent across CKD stages, potential confounding factors, such as palliative care settings and mobility issues warrant careful consideration.

Conclusion: The study underscores the importance of understanding and addressing musculoskeletal disorders in the CKD population, emphasizing the need for tailored interventions and future research endeavors.

KEYWORDS:
Musculoskeletal disorders, musculoskeletal pain, chronic kidney disease, end-stage kidney disease, hemodialysis patients

INTRODUCTION

Chronic kidney disease (CKD) is a leading cause of global mortality and has significantly contributed to the increasing burden of disability-adjusted life years (DALYs) over the past three decades. As of 2022, it is estimated that CKD affects more than 10% of the global population, impacting over 800 million individuals.[1-4] This condition is more prevalent among the elderly, women, ethnic minorities, and individuals with diabetes mellitus and hypertension. Globally, CKD poses a substantial burden, particularly in low- and middle-income countries (LMICs), where the age-standardized prevalence is 10.6% for men and 12.5% for women. Given the high prevalence of CKD and its associated adverse outcomes, there is an urgent need to enhance preventive measures and refine treatment strategies.[1-5]

Musculoskeletal disorders (MSD) are commonly associated with chronic kidney disease (CKD), including end-stage kidney disease (ESKD). MSD affects the bones, joints, muscles, and connective tissues, posing significant challenges due to altered bone metabolism, mineral imbalances, and other physiological changes linked to kidney dysfunction. Approximately 18 years ago, the Kidney Disease: Improving Global Outcomes (KDIGO) organization introduced a novel terminology to encompass this broad spectrum of clinical manifestations, termed Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD). According to KDIGO 2017, CKD-MBD is characterized by: (i) abnormal metabolism of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D; (ii) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (iii) soft-tissue calcifications, either vascular or extra-osseous. Patients with CKD-MBD frequently lack noticeable symptoms and typically present late. Many of these symptoms are non-specific, with the most frequent presentations including bone pain, arthralgia, proximal muscle weakness, tendinopathy, and spontaneous tendon rupture.[6]

Alterations in mineral metabolism and changes in bone structure are observable in all patients with CKD. In individuals undergoing dialysis, the entire musculoskeletal system—including bones, joints, muscles, tendons, and bursa—may be affected, with many patients showing signs of multiple types of musculoskeletal involvement.[7,8] The high burden of musculoskeletal diseases in this group can be attributed to several factors, including peripheral neuropathy, disrupted vitamin D metabolism,

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hyperparathyroidism, carnitine deficiency, aluminium toxicity, potassium imbalances (both hypo- and hyperkalaemia), acidosis, excessive iron accumulation, and severe hyperphosphatemia.[9]

Renal osteodystrophy, characterized by abnormal bone histology, is a key component of the bone abnormalities in CKD-MBD.[6] In CKD, abnormalities in bone remodelling, mineralization, and material properties develop, leading to significant decreases in structural strength, fractures, and deformities associated with long-term disease. Bone biopsy remains the gold standard for diagnosing and classifying renal osteodystrophy. Bone abnormalities in CKD can manifest as high turnover bone disease, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy.[6] These abnormalities result in increased bone fragility, leading to fractures. Therefore, understanding the prevalence and impact of musculoskeletal disorders in CKD patients is essential for providing comprehensive care and improving patient outcomes.

MATERIALS AND METHODS

Objectives

This study employs a systematic literature review to achieve two primary objectives (1) to explore the spectrum of disorders including osteoporosis, osteoarthritis, fibromyalgia, bone pain, and other relevant musculoskeletal conditions; and (2) to identify the range of prevalence rates of musculoskeletal disorders and main symptoms within various subpopulations of CKD patients. The secondary objective is to identify gaps and limitations in the current literature on musculoskeletal disorders in ESKD and to propose potential avenues for future research, including studies on novel therapeutic interventions, long-term outcomes of management strategies, and approaches tailored to specific patient subgroups.

Search strategy

A systematic literature search was conducted in the electronic databases PubMed, Embase, Scopus, and Cochrane Library. The search strategy utilised relevant keywords and Medical Subject Headings (MeSH) terms to comprehensively retrieve studies related to musculoskeletal disorders and ESKD.

Study selection criteria

The inclusion criteria encompassed studies that were published in peer-reviewed journals which involved adult individuals with CKD and/or musculoskeletal symptoms. Both observational studies (cross-sectional, cohort, case-control) and interventional studies (clinical trials, interventions) were considered. The exclusion criteria pertained to studies that were not published in English, those focusing exclusively on non-CKD populations, and studies with small sample sizes or incomplete data.

Data extraction, synthesis and analysis

The data extraction was conducted independently by three reviewers using a standardised form. The extraction fields included the study characteristics (author, year, country(ies), objective, design, sample size, patients' demographics), patients' CKD stage(s), musculoskeletal disorder types, prevalence rates, and the most common symptoms. A narrative synthesis approach was employed to summarise and integrate the findings across the selected studies.

Quality assessment

The quality of included studies was assessed using established tools such as the Newcastle-Ottawa Scale for Observational Studies and the Cochrane Collaboration Risk of Bias Tool for interventional studies. This assessment helped ensured the validity and reliability of the evidence synthesized. A critical appraisal was conducted for each study by two authors of this paper.

RESULTS

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the screening process is depicted in Figure 1.

Study characteristics

The 13 studies selected were conducted in Africa, Western Europe, East and West Asia. Four studies were undertaken in Egypt, and two in both France and Taiwan. Singular studies were conducted in Ethiopia, Spain, Denmark, and Iran. Furthermore, a comprehensive meta-analysis was included, encompassing data from 38 different countries. The predominant research method (11 out of 13 studies) was cross-sectional in nature. Additionally, there was one prospective cohort study and one meta-analysis, which incorporated data from 116 studies involving a total of 40,678 participants across 38 countries. The majority of the meta-analysis studies originated from the United States (18 studies) and the United Kingdom (12 studies). In the remaining 18 studies, the number of participants varied from 377 to 1169.[10] The participants were CKD patients over 18 years from both sexes (with a slight bias towards men) and mean ages ranging from 20[11] to 67.5.[12]

Patients' CKD stages

The 13 studies focused on different sub-populations with varying CKD stages. Seven studies focused on patients undergoing haemodialysis (different vintage),[12,13,14,15,7] including one study only with ESKD patients.[11] Two studies were done with pre-dialysis patients,[16,13] one study with patients with early and late-stage CKD not undergoing hemodialysis,20 and three studies with patients with different CKD stages undergoing dialysis or not.[17-19]

Musculoskeletal symptoms

The most common symptom recorded in the 13 studies was musculoskeletal pain which included arthralgia, myalgia, limb pain, and muscle weakness. The prevalence of arthralgia, which was the most common musculoskeletal manifestation, varied from 25.3%[12] to 83%[13], and it was reported across studies with patients with different CKD stages.

One study[13] with ESKD patients showed that the frequency of musculoskeletal symptoms increased with haemodialysis vintage, patients' age, and it was higher in men vs. women. Similarly, another study[12] showed, through logistic regression, that musculoskeletal symptoms were significantly associated

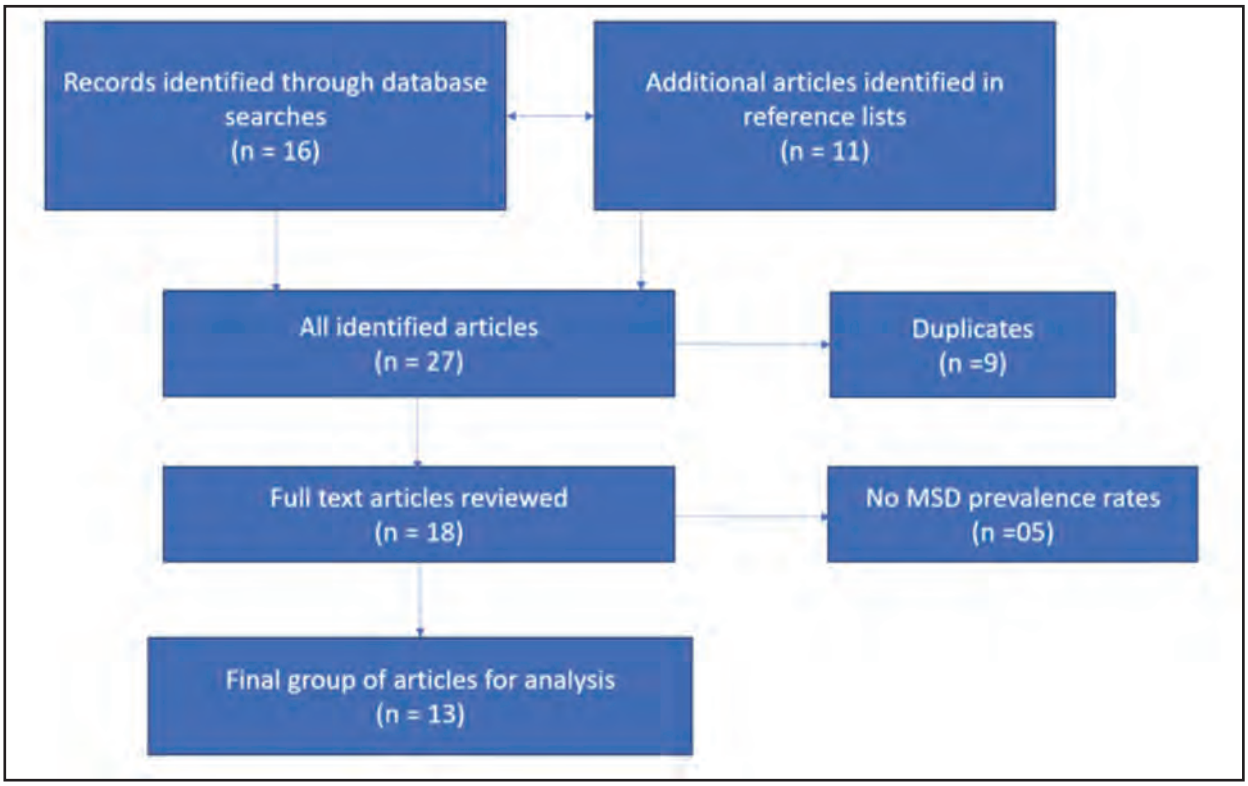

Fig. 1: PRISMA diagram of the screening process

with both dialysis vintage (odds ratio (OR) = 1.97; 95% CI 1.004–1.288, p = 0.044) and age (OR = 1.044, 95% CI 1.003–1.08, p = 0.035). The same study suggested that the threshold for the onset of musculoskeletal symptoms is around the seventh year of haemodialysis. Dialysis vintage was associated with the diagnosis of osteoarthritis, fractures, and chondrocalcinosis.

Several studies[16,20] have indicated that the prevalence of musculoskeletal pain remains consistent across all stages of CKD, suggesting no association between musculoskeletal pain and the risk of CKD progression. A potential confounding factor contributing to this outcome is the inclusion of CKD patients in stage 5 within palliative care settings, where chronic pain is actively managed.[19] Building upon this evidence, another study[10] contributed to further insight, demonstrating that chronic pain exhibits heightened severity in patients with advanced CKD.

Impaired mobility has also been correlated with musculoskeletal pain, as evidenced by a study conducted in Denmark[18] that compared CKD patients without mobility issues to the general population. Upon demographic matching, no difference in musculoskeletal pain was observed between CKD patients with mobility restrictions and the general population (61% and 63%, respectively; p=0.533).

Musculoskeletal disorders

The most common musculoskeletal disorders diagnosed clinically, as shown in the various studies were osteoarthritis (17.2%[13] and 53.9%[12]), osteoporosis (24.5%[11]), fibromyalgia (11%[19] and 51%[14]), carpopedal spasm (50.4%[7]), chronic musculoskeletal chronic pain syndrome (CMP) (38%)[11] and carpal tunnel syndrome (14.9%).[13] The most common radiologically diagnosed musculoskeletal disorders were secondary hyperparathyroidism (SHPT) diagnosed by X-ray[11] and Achilles Tendinopathy (67.9%), diagnosed by musculoskeletal ultrasonography (MSUS).[11]

Except for CMP, all musculoskeletal disorders were diagnosed among the haemodialysis population. One study[17] demonstrated, through logistic regression, that musculoskeletal disorders are most prevalent among women (AOR = 0.49; 95% CI 0.26, 0.94), with ages between 40-49 (adjusted odds ratio (AOR) = 3.34; 95% CI 1.07, 10.44) and CKD stages 3 (AOR = 0.24; 95% CI 0.06, 0.89) and stage 4 (AOR = 0.24; 95% CI 0.06, 0.89). Another study[11] similarly found that CMP was more prevalent in women compared to men (49 vs 28%, p<.001).

Prevalence rates

The prevalence of musculoskeletal disorders varied between 38%[11] and 90%[15]. This broad prevalence range can be attributed to differences in the definitions of musculoskeletal disorders, data collection methods, study designs, the scope of included musculoskeletal conditions, and the varying stages of CKD considered.

A sub-group analysis revealed that the highest prevalence of musculoskeletal disorders was found in studies with patients undergoing haemodialysis (60.4%[13] to 90.0%[15]) compared to pre-dialysis and CKD patients not undergoing dialysis (38.0%[9] to 64.0%[18]).

DISCUSSION

Musculoskeletal Symptoms

From the literature review, the most frequent musculoskeletal symptoms observed in various research studies were musculoskeletal pain, encompassing conditions like arthralgia (25.3%[12] to 83%[13]), myalgia, and limb discomfort reported across studies with patients with different CKD stages.

Chronic pain affects approximately 10–20% of the general adult population[21-24] with a notably higher prevalence among older women, with physical factors (such as obesity and other co-morbidities), emotional factors (like separation, divorce and widowhood), psychological factors (including anxiety and depression), and social factors (education, employment, and income) exerting significant influence.[23] Approximately 50–70% of these pain conditions are attributed to musculoskeletal origins, which would indicate that around 5–14% of the population experiences chronic musculoskeletal pain.[21-23]

Both patients undergoing dialysis[25-27] and those in the pre-dialysis stages of CKD[16,28,29] commonly experience musculoskeletal pain. Various factors can contribute to chronic musculoskeletal pain; potential culprits include gout, renal bone disease, and ischemic bone pain.[16,28] Research has demonstrated a significant connection between calcium × phosphate product levels and chronic musculoskeletal pain. Disruptions in calcium and phosphate balance, deficiency in vitamin D, and hyperparathyroidism have all been established as substantial underlying causes.[16,30]

Musculoskeletal Disorders

Osteoarthritis

The literature review showed that osteoarthritis was the most common musculoskeletal disorder among CKD patients. Within the CKD population, the prevalence of osteoarthritis surpassed that expected within the general population of similar age groups.[12,31] In these disorders, the knee joint was most frequently affected, followed by the ankle joint.[11,12,13,15,32]

Osteoporosis and fracture risk

Osteoporosis, characterized by a reduction in bone mineral density and deterioration of bone microarchitecture, is a significant concern in individuals with CKD. The literature review identified osteoporosis was diagnosed in one in four CKD patients.

The complex interplay of factors such as altered bone metabolism, hormonal imbalances, and mineral disturbances associated with kidney dysfunction contributes to the increased risk of osteoporosis in this population. Therefore, CKD patients are predisposed to fractures, adding a substantial burden to their overall health.

The risk of fractures in CKD is multifactorial, with factors such as mineral and bone disorders, impaired renal function, and comorbid conditions playing pivotal roles. Mineral imbalances, including disturbances in calcium and phosphorus metabolism, can compromise bone strength and integrity. SHPT, commonly observed in CKD, further exacerbates bone fragility. Additionally, the use of certain medications in the management of CKD, such as glucocorticoids, can contribute to bone loss and increase the susceptibility to fractures.[33-35] The consequences of fractures in CKD extend beyond the immediate physical impact, often leading to reduced mobility, impaired quality of life, and increased mortality risk.

Secondary Hyperparathyroidism

The most common radiologically diagnosed musculoskeletal disorders in the review was SHPT. The prevalence of SHPT in CKD is well-documented, with estimates ranging from 20% to 80%,[36] depending on the severity of the chronic kidney disease. SHPT emerges as a significant complication in the context of CKD, marked by high levels of blood parathyroid hormone (PTH). The development of SHPT in CKD is a result of abnormalities in various biochemical parameters, including elevated serum phosphorus and fibroblast growth factor 23 (FGF23), alongside reduced levels of serum calcium and vitamin D.[35]

SHPT emerges as the most prevalent diagnosis of musculoskeletal diagnosis detected radiologically.[11,16,33,34] Research indicates that anomalous radiographic indicators of SHPT escalate with the duration of dialysis. Common manifestations include sub-periosteal resorption of terminal phalanges, osteosclerosis (notably "rugger-jersey spine"), and the occurrence of brown tumors.[11,16,33,34]

Tendinopathies

Achilles Tendinopathy was also identified in the systematic review. Tendon tenderness and tendon ruptured have been reported in the literature among ESRD patients. The most common is Achilles tendon tenderness on palpations with prevalence varies between 11.9% to 44%.[37-38] Achilles tendinopathy was the most frequent condition detected MSUS followed by quadriceps and patellar tendinopathies.[11] The ultrasonographic abnormalities findings in Achilles tendinopathy include tendon thickness (>6mm), followed by reduction in echogenicity and the presence of calcified areas.[11,16] For quadriceps tendinopathy, the most prevalent abnormalities on MSUS were reduced echogenicity, followed by tendon thickness (>6 mm), and the presence of calcified areas.[11,37,39]

Renal Amyloidosis and Carpal Tunnel Syndrome

Dialysis-related amyloidosis (DRA) is a known dialysis complication with musculoskeletal involvement. In musculoskeletal DRA, there is a chronic accumulation of B2-microglobulin in the bone, muscle, periarticular cartilage, ligament and synovium. B2-microglobulin is a middle molecule of uremic toxins excreted in the urine. However, anuric patients on dialysis have a marked accumulation of these middle molecules due to poor removal during dialysis. The typical presentation is carpal tunnel syndrome (CTS), scapula-humeral peri-arthritis, tenosynovitis and bone cysts. Patients typically complain of numbness over the median nerve distribution and shoulder pain.[40] Jokar et al. reported a CTS prevalence of 24.3% in the haemodialysis population.[12]

Knowledge gaps and Limitations

In recent years, musculoskeletal disorders research in the context of CKD, including ESKD, has gained momentum, shedding light on the complex interplay between renal dysfunction and skeletal health. Despite the growing body of literature, notable gaps and limitations still exist, which warrant further investigation to comprehensively understand and effectively address the musculoskeletal challenges faced by individuals with ESKD.

A key area with a paucity of qualitative research is the realm of novel therapeutic interventions explicitly tailored for musculoskeletal disorders in ESKD. While there has been progress in elucidating the mechanisms underlying bone and muscle abnormalities in ESKD, innovative and targeted interventions to mitigate these issues remain limited. Another gap is the dearth of qualitative studies examining cutting-edge therapy interventions specifically designed for musculoskeletal issues in the ESKD population. This knowledge gap of efficient and focused interventions to address the complex musculoskeletal problems presented by ESKD patients remains because the majority of the published research concentrates on prevalence rates and related characteristics.

Additionally, the long-term outcomes of management strategies for musculoskeletal disorders in ESKD remain relatively under explored. Many existing studies tend to focus on short-term interventions and outcomes, leaving a gap in our understanding of the durability and sustainability of the implemented management approaches. Investigating the extended effects of interventions, and assessing their impact on long-term bone density, muscle function, and overall quality of life, could provide valuable insights into optimising treatment plans and refining therapeutic strategies for individuals living with ESKD-related musculoskeletal issues.

Furthermore, there is a knowledge gap about the implementation of management practices that are durable and sustainable because the majority of the research concentrates on short-term interventions and instant results.

Future Research Directions

An avenue with high potential for exploration is research tailored to specific patient subgroups within the ESKD population. The impact of musculoskeletal disorders can vary according to age, co-morbidities, and dialysis modality. Therefore, targeted investigations into how these factors interact with the musculoskeletal health of ESKD patients could unveil tailored intervention approaches. By accounting for these nuances, researchers can develop more precise and effective strategies to improve the quality of life for subgroups that might be disproportionately affected by musculoskeletal challenges.

Future research projects should give top priority to the creation and assessment of treatments that go beyond conventional management techniques. To address musculoskeletal problems in ESKD, novel treatments like pharmacological drugs, physical therapy, or regenerative strategies must be investigated in order to offer complete and customised solutions. Examining the effectiveness, safety, and patient compliance with these therapies may expand the range of treatments that are accessible and have a major influence on the quality of life for people with musculoskeletal issues associated with ESKD.

Moreover, future research endeavours ought to give precedence to longitudinal studies that monitor the prolonged impacts of therapies, evaluating their influence on the long-term quality of life, muscular function, and bone density of persons suffering from ESKD. This long-term methodology would offer significant insights into improving therapy approaches and treatment programmes for long-term gains in musculoskeletal health.

Lastly, studies that focus on particular patients' subgroups within the ESKD population are required. Musculoskeletal diseases can have different effects depending on age, gender, dialysis mode, and co-morbidities. Exact research on the interactions between these variables and musculoskeletal health in people with ESKD may provide specific management strategies. Researchers can create more targeted and effective interventions to enhance the quality of life for populations that may be disproportionately impacted by musculoskeletal issues by taking these subtleties into account. This method guarantees that interventions take into account the various demands of the ESKD population in addition to being effective.

CONCLUSION

Musculoskeletal disorders pose a substantial burden on CKD patients, exhibiting varied prevalence rates and associated symptoms across different stages of the condition. This systematic review aims to consolidate existing knowledge regarding musculoskeletal disorders in CKD patients, pinpoint gaps and limitations in current literature, and propose promising directions for future research. By addressing these gaps and exploring avenues such as innovative interventions, evaluating long-term outcomes, and adopting subgroup-specific approaches, the research community can enhance comprehension, management, and ultimately, the quality of life for individuals navigating the complex interplay of musculoskeletal health and CKD.

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COMMENTARY

Recommendations for enhancing research outcomes and the efficacy of transcranial direct current stimulation in post-stroke motor rehabilitation for local settings

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ABSTRACT

Transcranial direct current stimulation (tDCS) has emerged as a potential adjunct therapy for post-stroke motor rehabilitation. While conventional rehabilitation methods remain the primary approach to improving motor function after stroke, many patients experience incomplete recovery, necessitating the exploration of additional interventions. This commentary article examines the role of tDCS in post-stroke motor recovery, focusing on its mechanisms, efficacy, and limitations. Herein, the variability in research findings and individual patient responses as well as the recommended methods for optimising tDCS use in local clinical settings are highlighted.

KEYWORDS:
Transcranial direct current stimulation, non-invasive brain stimulation

INTRODUCTION

Post-stroke motor impairment is a common consequence of ischaemic and haemorrhagic stroke, affecting millions of people worldwide. Motor deficits, including weakness, spasticity, and impaired coordination, lead to significant disability and reduced quality of life.[1] Conventional rehabilitation, which aims to mitigate these deficits, primarily involves physical (PT) and occupational therapy (OT). However, despite prolonged rehabilitation, many stroke survivors experience limited functional recovery, necessitating adjunctive therapies.

Transcranial direct current stimulation (tDCS) is an emerging non-invasive brain stimulation technique that has demonstrated the potential to enhance neuroplasticity and motor recovery in stroke patients.[2] While early research suggests promising outcomes, challenges such as individual variability and inconsistent findings continue to hinder its widespread application.

In Malaysia, the adoption of tDCS as an adjunctive therapy for post-stroke motor recovery as well as the availability of local research on this technique remain limited. To the best of the author's knowledge, this service is currently available in only a few teaching hospitals, private hospitals, and one government rehabilitation centre. However, there is no information regarding its use in Ministry of Health hospitals. To date, only one case series and a technical report from the Ministry of Health have been published, and only one tDCS model for research purposes is registered with the Malaysia Medical Device Authority. This limited adoption and research base highlight the need for greater awareness, resources, and local studies to explore the potential of tDCS in improving stroke rehabilitation outcomes in Malaysia.

ROLES OF tDCS

tDCS is a cost-effective, portable, and user-friendly alternative to transcranial magnetic stimulation (TMS), enhancing its accessibility for clinical applications. It is generally well-tolerated, with minimal reported side effects. Notably, no seizures associated with tDCS have been documented in the literature to date.

tDCS delivers low-intensity electrical currents via electrodes placed on the scalp, thereby modulating cortical excitability.[2] By altering neuronal excitability, this procedure promotes neuroplasticity and potentially enhances the brain's capacity for motor learning and recovery.[2,3] Depending on electrode placement and current polarity, tDCS can either increase or decrease the excitability of targeted brain regions, facilitating long-term potentiation (LTP) or depression (LTD), both of which are critical in neuroplasticity.[4]

In post-stroke motor rehabilitation, tDCS typically targets the motor and premotor cortices, aiming to stimulate the areas involved in motor function. Several studies have demonstrated that tDCS can aid in motor recovery by improving the brain's ability to reorganise and form new neural connections, leading to positive outcomes in upper limb mobility, gait, balance, and spasticity.[1,2,4-7] Notably, combining this procedure with task-specific motor activity has been shown to amplify its effects.[5,6] For instance, tDCS combined with PT or OT often results in more significant improvements in motor function than when either therapy is used alone.

CHALLENGES

Despite these encouraging findings, several challenges limit the widespread adoption of tDCS in post-stroke motor rehabilitation in Malaysia. Specifically, these challenges can be divided into general and local settings.

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i) Technological and Methodological Gaps

The main challenge faced by most healthcare professionals using tDCS is the inconsistency in research results regarding the overall efficacy of tDCS.[8] While some studies demonstrated substantial benefits, others reported little to no improvement in patient outcomes. This inconsistency can be attributed to diverse biological and patient factors. Biological differences among patients, such as variations in cortical pyramidal cell orientations and their cortical layers,[9] as well as synaptic neurotransmitter concentrations,[3] could impact how tDCS affects neuroplasticity. Patient heterogeneity, such as differences in stroke location, severity, and time since onset, further complicates the predictability of outcomes.

Procedural differences can also exacerbate these inconsistencies. Variations in study design, such as differences in electrode placement, stimulation intensity, and session duration, can result in variable outcomes. These factors make it difficult to standardise protocols and draw definitive conclusions regarding the effectiveness of tDCS across different patient populations.

Compared to TMS, tDCS offers less spatial and temporal precision, which limits its ability to target specific brain regions with high accuracy. The effects of tDCS are typically more subtle and often require multiple sessions to achieve clinically significant outcomes. To address these limitations, advanced navigation tools such as high-definition tDCS (HD-tDCS) have been developed. HD-tDCS allows for the precise delivery of direct currents to both cortical and deeper brain structures, improving the accuracy and effectiveness of stimulation. Despite its potential advantages, the adoption of HD-tDCS in Malaysia remains limited, primarily due to the substantial costs associated with the technology. As a result, alternative approaches, such as using neuroimaging to enhance the precision of electrode placement, are often favoured.

ii) Limited Availability of tDCS Services in Local Settings

The availability of tDCS services across Malaysia remains limited, particularly within public healthcare facilities. Non-invasive brain stimulation techniques, including tDCS, have yet to gain widespread recognition as a standard component of stroke management. This lack of integration into neurorehabilitation programmes restricts access for many patients who might benefit from its application. The scarcity of accessible tDCS services poses a significant challenge, hindering the delivery of comprehensive neurorehabilitation and limiting opportunities for recovery in post-stroke patients.

iii) Trained Personnel for Administering tDCS

A significant challenge in the utilisation of tDCS is the shortage of healthcare providers adequately trained in its administration. Inadequate training can result in improper application, leading to suboptimal patient outcomes or potential adverse effects, thereby compromising patient safety and undermining confidence in tDCS as a therapeutic option. Furthermore, the effective use of tDCS requires the careful selection of suitable candidates, a process that demands thorough assessments by experienced specialists in the field of neuroscience and brain stimulation techniques. These challenges highlight the need for structured training programs and credentialing systems to ensure that healthcare providers are equipped with the necessary skills and knowledge to safely and effectively deliver tDCS. Strengthening professional competence in this area is essential for maximizing the therapeutic potential of tDCS while maintaining high patient care standards.

iv) Lack of Local Research and Publications

The scarcity of locally conducted research and publications on tDCS in Malaysia presents a significant barrier to its utilisation in clinical practice. This gap limits the development of evidence-based approaches tailored to the specific needs and characteristics of the local population and makes it challenging to effectively advocate for the adoption of tDCS in healthcare settings. Moreover, the lack of comprehensive studies on cost-effectiveness, long-term outcomes, and safety further impedes its widespread implementation. Addressing this issue requires prioritizing local research initiatives and fostering collaborations among clinicians, researchers, and academic institutions to build a stronger evidence base for tDCS within Malaysia's healthcare system.

RECOMMENDATIONS

Several strategies can be implemented to address these challenges and improve research outcomes and the efficacy of tDCS in post-stroke motor rehabilitation in Malaysia.

i) Patient-Specific Assessment and Protocol

a) Individualised Assessment: Given the biological variability among patients, a thorough evaluation of neuronal damage after stroke is crucial. In the absence of advanced navigation tools in our local clinical and research settings, a strong foundation in neuroanatomy and the interpretation of neuroimaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), becomes indispensable for precise electrode placement. Pre-stimulation neuroimaging, combined with comprehensive clinical assessment, should be employed to determine the location and extent of lesions. A deep understanding of neuroanatomy and motor representation, particularly the homunculus, is invaluable in guiding electrode positioning and optimising targeted stimulation, thereby enhancing the likelihood of a favourable response. Moving away from a single standardized, one-size-fits-all approach, such as universally stimulating the contralateral C3 and C4 regions for motor weakness irrespective of the severity of neuronal damage, is essential for achieving better outcomes.

b) Patient-Specific Protocols: Tailoring tDCS protocols to individual patients is vital. Factors, such as stroke severity, time since onset, and specific motor impairments, should be considered when designing treatment plans. Standardised scales, such as the Medical Research Council (MRC) scale for motor strength, the Fugl-Meyer Assessment for motor function, and the Modified Ashworth Scale for spasticity, should be used to document patient progress and employ appropriate treatment adjustments. Accurate documentation of patient characteristics and treatment protocols, including the device used, is also essential for facilitating comparisons between institutions and improving research outcomes.

ii) Combining tDCS with Conventional Therapy

The combination of tDCS with PT or OT can significantly enhance the efficacy of the procedure. Research suggests that the synergistic effect of pairing brain stimulation with active motor tasks amplifies neuroplasticity, facilitating greater functional recovery.[5,6] Studies have demonstrated that administering tDCS during rehabilitation exercises ('online') or immediately afterward ('offline') optimises recovery outcomes by targeting the brain's heightened responsiveness to therapy during these periods.

iii) Enhance Training and Skill Development

The development and implementation of comprehensive training programs and certifications for healthcare providers, including both medical practitioners and paramedics, are fundamental to expanding the use of tDCS in clinical and research settings. These programs should focus on equipping participants with the theoretical knowledge and practical skills necessary for safe and effective tDCS delivery. Continuous education initiatives, such as interactive workshops, online courses, and hands-on training sessions, are essential to keep providers updated on the latest advancements in tDCS technology, emerging applications, and evidence-based practices. Disseminating new findings and treatment protocols through these platforms will enhance providers' competency and confidence in applying tDCS. Furthermore, fostering international collaboration with global experts and leading institutions can bring advanced training modules and best practices to Malaysia. Such partnerships not only improve the quality of training but also enable knowledge exchange and exposure to innovative methodologies.

iv) Foster Research and Publications

Promoting collaboration among universities, clinical institutions, and international partners is essential to advancing tDCS research and addressing knowledge gaps. Priority research areas should include investigating factors that contribute to individual variability in treatment response, and developing refined, personalised treatment protocols that can be effectively implemented on a larger scale. Moreover, supporting academic publications and disseminating findings through peer-reviewed journals can strengthen evidence-based practices. Where resources allow, advanced imaging techniques, such as quantitative electroencephalography (QEEG) and diffusion tensor imaging (DTI) tractography, could be utilised to better identify the target areas for stimulation, thereby improving the accuracy and outcomes of tDCS interventions.

v) Expand Accessibility to tDCS Services

Expanding tDCS services in public healthcare institutions is essential to improve accessibility for patients. To further broaden the reach of these services, fostering public-private partnerships can play a pivotal role, enabling collaboration between sectors to enhance resource allocation and service delivery. Additionally, the establishment of a national multidisciplinary tDCS task force comprising clinicians and researchers could help address service gaps and define research priorities. Establishing clear referral guidelines to streamline interdisciplinary referrals for stroke patients to receive tDCS treatment will further promote its clinical adoption. Such measures are key to improving accessibility, awareness, and the effective use of tDCS, ultimately enhancing outcomes in post-stroke motor recovery.

CONCLUSION

tDCS represents a promising adjunctive therapy for post-stroke motor rehabilitation that potentially enhances motor recovery through neuroplasticity. However, challenges related to inconsistent research findings, individual variability, and limited accessibility must be addressed. By implementing individualised treatment protocols, integrating tDCS with conventional therapies, and fostering greater awareness and training among healthcare professionals, this technique can be effectively incorporated into stroke rehabilitation programs. Continued research and collaboration are essential to optimise its use and provide additional treatment options for functionally impaired stroke survivors.

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33. Prof Datin Dr Zunaina Embong