Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 78

Issue No: 3

May 2023

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

MJM

Official Journal of the Malaysian Medical Association

Volume 78 Number 3 May 2023

EDITORIAL BOARD

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

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

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Printed by: Digital Perspective Sdn. Bhd.
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Original Articles

CONTENTS Page

The effect of medical education and counselling on treatment adherence and disease severity in patients with acne vulgaris: a non-randomised interventional study

Wee Yun Ling, MRCP (UK)[1], Chai Har Loo, AdvMDerm[1], Nurul Shafaril Niza Mohd Akhir, BPharm (Hons)[2], Jo Lyn Tan, MPharm[2], Norazlima Mohd Ali, AdvMDerm[1], Wooi Chiang Tan, AdvMDerm[1]

[1]Department of Dermatology, Hospital Pulau Pinang, Penang, Malaysia, [2]Department of Pharmacy, Hospital Pulau Pinang, Penang, Malaysia

ABSTRACT

Introduction: Acne vulgaris (AV) is a common inflammatory skin disease affecting adolescents and young adults. It affects one's self-esteem and social relationship. In addition, poor adherence to treatment can cause poor treatment response and disease recurrence. This study aims to determine the effectiveness of medical education and counselling on treatment adherence and disease severity.

Methods: This is a non-randomised interventional study with age- and treatment- matched control conducted in a tertiary dermatology clinic from July 2021 to June 2022. Patients in the intervention group received a 10 min video presentation on acne, followed by treatment counselling. The adherence rate was determined objectively (pill counting and tube weighing) and subjectively (ECOB questionnaire). The disease severity was assessed using the Comprehensive Acne Severity Scale (CASS) and Global Acne Grading System (GAGS).

Results: A total of 100 patients completed the 12-week study. With intervention, patients have better adherence to topical medication (5% benzoyl peroxide gel: 71% vs 57.9%, p= 0.031; 0.05% tretinoin cream: 58.7% vs 45.4%, p= 0.044) at week 12. However, the intervention program did not improve adherence to oral medication. Overall, with intervention, a significantly higher percentage of improvement in disease severity was noted (47.3% vs. 39.1%, *p*=0.044). Non-adherence to treatment was attributed mostly to forgetfulness in 54% of the patients, followed by a busy lifestyle (41%) and little knowledge of acne (26%).

Conclusion: Patients have significantly better adherence to topical medication with education and counselling. Better adherence to treatment leads to more remarkable disease improvement.

KEYWORDS:
Acne, counselling, disease severity, education, treatment

INTRODUCTION

Acne vulgaris (AV) is a common inflammatory skin disease affecting adolescents and young adults. Acne lesions affect one's self-esteem and social relationship. As a result, those affected can experience difficulty at work and in social interaction.

Treatment for AV is widely available. The cause of failure to respond to therapy or relapse of disease is often due to poor adherence to treatment. Adherence to acne medication has been as low as 12.5% for the past 40 years.[1] One study reported poor adherence worldwide, with the worst rate in Europe (58%) than in Asia (48%) and America (43%).[2]

Multiple factors have been identified that can influence one's adherence to acne treatment. These include age, gender, education level, employment status, lack of acne knowledge, lack of satisfaction with treatment, treatment tolerability, frequency of follow-up visits and the doctor-patient relationship.[2-6]

Disease education and medication counselling are essential components during a daily clinic consultation. Nevertheless, many clinicians do not perform well in these two areas due to heavy clinic workloads and limited time. This study aims to determine the effectiveness of medical education and counselling on treatment adherence and disease severity. The secondary objective was to identify the risk factors affecting treatment adherence.

MATERIALS AND METHODS

Patient Population and Study Procedures

This interventional study was conducted at the dermatology clinic, Hospital Pulau Pinang, between July 2021 to June 2022. It was a 12-week study with three clinic visits (weeks 0, 6, and 12). Inclusion criteria were patients with AV who were 13 years age or older. Exclusion criteria were an acneiform eruption of any other causes, a pregnant or lactating patient, psychiatric disorders and cognitive impairment. Sample size calculation, together with consideration from drop-outs, we recruited 100 patients for this study. Informed written consent was obtained from the participants or parents of minors before recruitment. The age- and treatment-matched control group was selected at a 1:1 ratio by a doctor who was not involved in this study. Subjects were evaluated at weeks 0, 6 and 12.

This article was accepted: 04 March 2023
Corresponding Author: Wee Yun Ling
Email: jenniferling85@gmail.com

Demography data was collected. An independent dermatologist assessed acne severity in weeks 0, 6 and 12 by using the Comprehensive Acne Severity Scale (CASS)[5] and Global Acne Grading System (GAGS).[8] Patients were prescribed with 5% benzoyl peroxide gel, 0.05% tretinoin cream, oral doxycycline or oral isotretinoin based on their acne severity. Throughout this study period, all the patients were allowed to use their own cleansers and moisturisers.

Medication adherence was assessed in weeks 0, 6 and 12 using the objective method (tube weighing and pill counting) and subjective method (ECOB questionnaire).[9] At week 12, patients must also answer a separate questionnaire containing reasons for non-adherence to treatment.

The intervention group was provided with a 10-min video presentation on AV, followed by individual treatment counselling by a pharmacist at week 0. The video answered the ten most frequently asked questions regarding acne. We adapted acne information from patient information leaflets developed by the British Association of Dermatologists.[10] During the counselling, the pharmacist would demonstrate the medication administration methods, explaining the possible side effects and their management. Patients were reassured of the importance of treatment adherence even though they noticed no immediate progress. In addition, an acne information leaflet was distributed to them to consolidate their understanding of acne.

This study was approved by the Ministry of Health Medical Research Ethics Committee and the National Medical Research Registry (NMRR-21-1487-60586). Also, permissions were obtained from the respective authors to use the questionnaires above.

Adherence Assessment

Topical treatment

The amount of topical treatment the patient should have used was determined by estimating the acne surface area using the patient's hand. One 'hand area' of the involved skin requires 0.5 finger-tip unit (FTU) or 0.25 g of ointment.[11] One FTU is the amount of ointment expressed from a tube with a 5 mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger. The patient was taught how to use the FTUs to manage treatment applications. Patients were given an adequate supply of topical medicine during the visits at weeks 0 and 6. We weighed the remaining topical gel/cream at subsequent visits at weeks 6 and 12 to ascertain the amount used. The formula to calculate topical medication adherence (MED AD) is: The actual weight of the medication used/the expected weight × 100%.

Oral treatment

Patients were supplied with the exact number of tablets during the visits at weeks 0 and 6. We did pill counting at subsequent visits in weeks 6 and 12. The formula to calculate oral MED AD is: The number of pills taken by the patient/the number of pills the patient should have taken × 100%.

ECOB Questionnaire

ECOB is a simple, validated questionnaire developed by Pawin et al.[9] There are 2 sets of questionnaires (topical and oral therapy) with 4 questions each. Patients are classified as poor adherers if one of their answers differ from the expected answer.

Disease severity Assessment

CASS questionnaire

This validated acne grading system incorporates a grading scale and lesion counting over the face, chest and back.[7] It is simple to use in clinical practice and strongly correlates with the Leeds grading. An assessor stands 2.5 m from the patient to assess acne disease severity. Acne severity is classified into grades 0 to 5 (clear to very severe).

GAGS questionnaire

This numerical grading system measured the acne severity over six locations: the forehead, left cheek, right cheek, nose, chin and chest and back.[8] Each type of acne is given a score (the comedone is 1; the papule is 2; the pustule is 3; and the nodule is 4). In addition, each location is given a factor: the forehead, left cheek; and right cheek are assigned a factor of 2; the nose and chin a factor of 1; the chest and upper back a factor of 3. The total score is the sum of all six regional scores: 1-18 is a mild disease; 19-30 is moderate; 31-38 is severe; ≥ 39 is very severe.

The percentage of improvement in acne disease severity at week 12 is calculated as: The difference between GAGS scores in week 12 and week 0 / GAGS score in week 0 × 100%.

Study Size

Until now, there has been no previous similar AV study with the same scoring system as we were doing. However, Bostoen et al.[12] had shown psoriasis disease severity and quality of life (QOL) improved significantly three months after the intervention group of patients underwent an educational program.[12] AV and psoriasis are chronic visible skin diseases that can be debilitating and affect one's QOL. The severity of both the conditions can range from mild, moderate and severe. Treatment for both the disorders involves topical and systemic, which need proper education and counselling to ensure treatment efficacy and better disease control. Hence, based on this paper, we used a G power calculator to count our sample size.

G* Power calculation 3.1.9.7 found that 90 patients were needed for this study. There is an 80% probability that the investigation would detect a treatment difference at a two-sided 0.05 significance level if the mean difference between treatments is 2 and the standard deviation is 2. An additional 10% is added to include possible drop-out cases. Therefore, the total sample required is 100 patients.

STATISTICAL ANALYSIS PLAN

IBM SPSS version 26 was used for statistical analyses. Categorical data were expressed as frequencies and percentages and analysed using the Pearson Chi-square test. The normally distributed continuous variables were summarised in mean and standard deviation, while the non-normally distributed variables were expressed as median and interquartile range. These data were analysed using an independent T-test and Mann-Whitney test. A multiple

logistic regression test was used to determine the association of factors affecting the adherence rate. The significance level was set as $p<0.05$.

RESULTS

Demographics

A total of 108 patients were assessed for eligibility at the dermatology clinic. Three patients did not fulfil the criteria so finally 105 patients were recruited. The age- and treatment-matched control group was selected at a 1:1 ratio. Five patients dropped out (three from the intervention group and two from the control group) during the study, leaving 100 patients successfully completed the 12-week study and proceeded with data analysis. There are no statistically significant differences in the demography between the intervention and control group. In the intervention group, two subjects moved to other cities to further their studies, whereby another one subject defaulted follow-up due to logistic reason. In the control group, one patient moved to another city due to job relocation and another one patient developed kidney disease and was put on immunosuppressants.

The mean age was 22.6 years. The median age of acne onset was 16 years, while the disease duration was 4 years. More than 50% of the patients in both the groups have a positive family history of acne and normal body mass index (BMI).

According to CASS, half of the participants in the intervention group had moderate acne, followed by mild acne (15, 30%) and severe acne (10, 20%). In the control group, 21 participants (42%) had moderate acne, 18 (36%) had mild acne and 11 (22%) had severe acne. Based on GAGS, the mean severity of acne in the intervention group was 21.2 ± 6.31 and 20.9 ± 6.98 in the control group.

Adherence rate

Table I shows the adherence rate between intervention and control groups at week 12. Based on the objective measurement, subjects in the intervention group had a better adherence rate in using 5% benzoyl peroxide gel compared to their counterpart in week 6 (74.6% vs 63.8%; $p=0.057$) and week 12 (71.0% vs 57.9%; $p=0.031$). Participants on 0.05% tretinoin cream also showed a significantly higher adherence rate in the intervention group in week 6 ($p=0.045$) and week 12 ($p=0.044$) compared to the control group. Subjects in the intervention group who received oral antibiotics or oral isotretinoin showed a higher adherence rate than the control group, but the difference was not statistically significant.

Based on the subjective measurement by ECOB, with intervention, patients on topical treatment were better adherers than the control group at week 12 ($p=0.022$). Although subjects who received oral therapy in the intervention group also had a higher number of good adherers, they were not statistically significant.

Disease Severity

Figures 1 and 2 show the comparison of disease severity based on CASS and GAGS between intervention and control groups on weeks 0, 6 and 12.

Patients showed improvement in disease severity in both, intervention and control groups at weeks 6 and 12. However, the difference between the two groups was statistically not significant. Thus, the degree of improvement in disease severity over the past 12 weeks was calculated. Patients in the intervention group had significantly greater improvement than the control group (median percentage of improvement 47.3% vs 39.1%, $p=0.044$).

Reasons for Non-adherence

Overall, 15 participants did not miss their medication throughout the 12 weeks of the study. For the remaining 85 participants (Figure 3), forgetfulness and a busy lifestyle were the two most common reasons for non-adherence to treatment (54% and 41%, respectively). The third most typical reason for non-adherence was little knowledge about acne (26%). Ten participants (12%) reported having adverse effects from topical medication, which included skin burning, stinging, redness, and dryness.

Factors affecting Adherence

There is no significant association of adherence with gender, age of onset, educational level, marital status, family history of acne, smoking status, type of acne, disease severity, knowledge about acne and patients' satisfaction.

The multiple logistic regression test showed that only two factors significantly affected good adherence. First, patients in the intervention group have 3.5 odds of better adherence to topical medication than their counterparts ($p=0.027$). However, the intervention did not improve adherence to oral medication ($p=0.480$). Secondly, those who believed the prescribed medication was effective also had better compliance (OR 5.12, 95% CI 1.19-22.10, $p=0.029$).

DISCUSSION

Demographics: The mean age of our subjects was 22.6 years, similar to a study done in the United Kingdom.[13] Dreno B et al.[2] showed that 47% of Asians had acne onset at 16-20 years, comparable to ours, which had a median age of 16 years. Although AV is not an inheritable disease, it inclines to occur in families.[2,14,15] Those with first-degree relatives with acne were more prone to moderate to severe, earlier onset and truncal acne.[14-16] Our study showed similar results where more than two-thirds of our participants had first-degree relatives with acne and were in the moderate-severe group. More than half of our study population had normal BMI. This finding supported previous studies that revealed no relationship between BMI and acne severity.[14,15,17]

Adherence Rate

Table II summarises previous literature on acne medication adherence.

We did tube weighing and pill counting to objectively assess the patient's adherence. Our subjects in the intervention group performed significantly better in treatment adherence than their counterparts. Myhill et al.[13] mentioned patient education material helped increase treatment adherence compared to more clinic visits and combination topical drugs.

Table I: Adherence rate between intervention and control groups at week 12

	Overall adherence n=100	Intervention n=50	Control n=50	*p* value
a) Objective measure				
5% benzoyl peroxide gel, %, mean (SD),	64.5%	71.0 (28.05)	57.9 (31.48)	0.031*
0.05% tretinoin cream, %, mean (SD)	51.9%	58.7 (28.73)	45.4 (23.92)	0.044*
Oral antibiotic, %, Median (IQR)	94.3%	95.2 (7.14)	94.6 (11.90)	0.551**
Oral isotretinoin, %, mean (SD)	96.1%	96.3 (4.91)	95.9 (4.51)	0.856*
b) Subjective measure (ECOB)				
Topical treatment, n (%)				
Good	81.0%	45 (90.0)	36 (72.0)	0.022‡
Poor		5 (10.0)	14 (28.0)	
Oral treatment, n (%)				
Good	41.9%	17 (45.9)	14 (37.8)	0.480‡
Poor		20 (54.1)	23 (62.2)	

*Independent T-test; ** Mann Whitney U test; ‡ Pearson Chi-square test;
§Total patient on oral medication was 74 people (37 in intervention, 37 in control group)

Table II: Literature review on acne medication adherence

Study; year; country	Sample size	Measurement methods	Topical adherence rate	Oral adherence rate
Ling et al. (current study) prospective case-control study 2022 Malaysia	100	Pill count and tube weighing ECOB questionnaire	5% BPO gel: 64.5%; Tretinoin cream: 51.9% ECOB: 81.0%	Oral antibiotic: 94.3%; Oral Isotretinoin: 96.1% ECOB: 41.9%
Zaghloul et al.[3] Objective assessment of compliance with treatments in acne 2005 UK	403	Pill count and tube weighing	Topical and oral medication other than Isotretinoin: 35.2%	Isotretinoin: 71.4%
Dreno et al.[2] Large-scale worldwide observational study of adherence with acne therapy 2010 France	3339	ECOB questionnaire, self/dermatologist questionnaire	Topical only: 60% Combination oral and topical: 56%	Isotretinoin: 54% Combination oral and topical: 46%
Miyachi et al.[4] Acne management in Japan 2011 Japan	428	ECOB questionnaire, self/dermatologist questionnaire	Topical: 48% Combination topical: 51%	Oral: 7% Combination oral: 14%
Myhill et al.[11] Use of supplementary patient education material increases treatment adherence and satisfaction among acne patients receiving Adapalene 0.1% benzoyl peroxide 2.5% gel in primary care clinical a multicentre, randomised, controlled clinical study 2017 UK	97	Medication event monitoring system (MEMS) caps	Topical + supplementary education material group: 63.1% Topical + more visits: 48.2% Topical alone: 56.5%	-

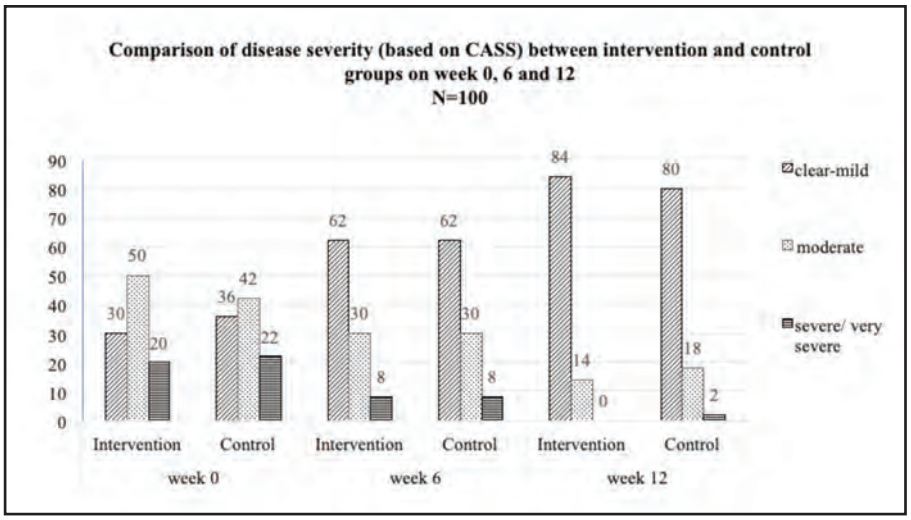

Fig. 1: Comparison of disease severity between intervention and control groups on weeks 0, 6 and 12 (based on CASS)

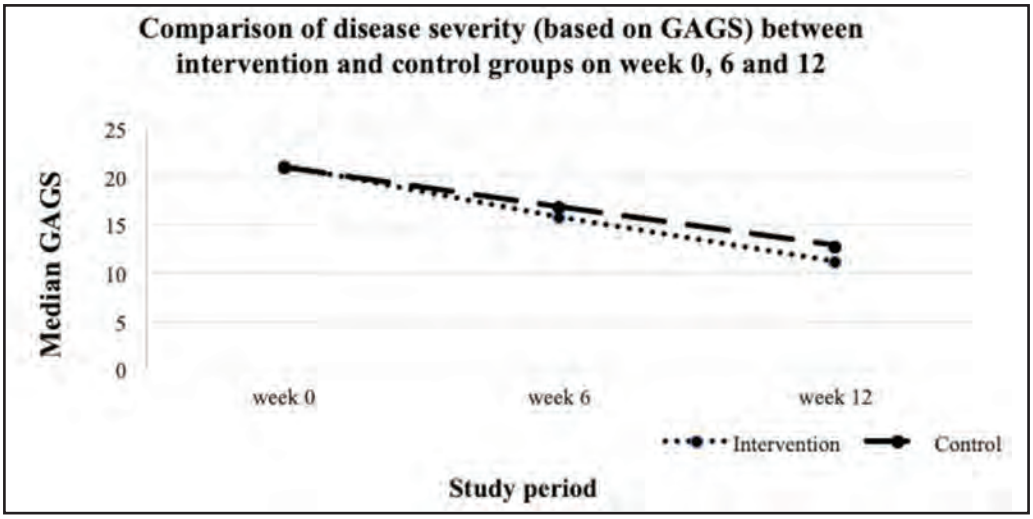

Fig. 2: Comparison of disease severity between intervention and control groups on weeks 0, 6 and 12 (based on GAGS)

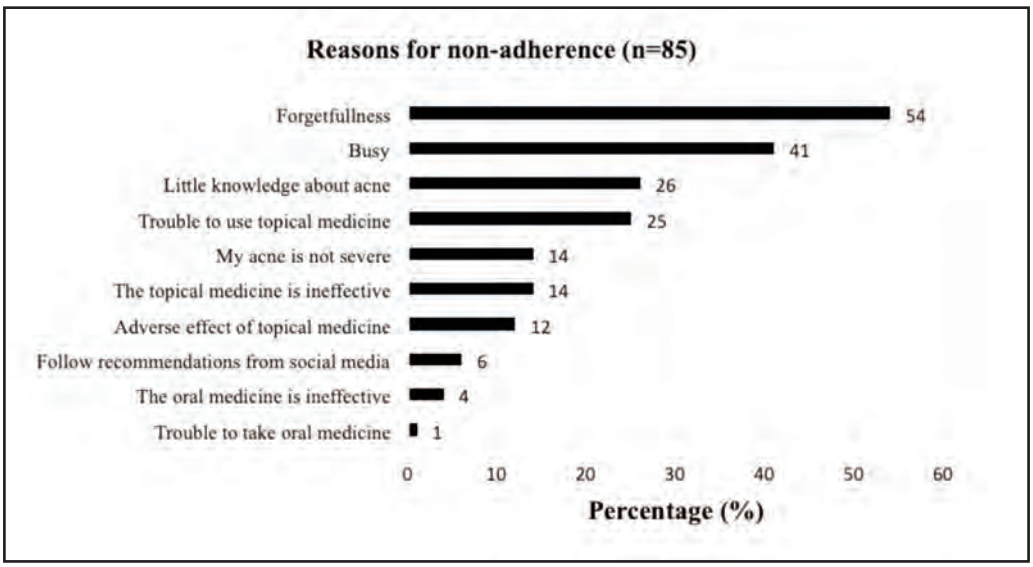

Fig. 3: Reasons for non-adherence

Using the pill counting method, both the intervention and control groups showed high adherence rates for oral antibiotic and isotretinoin throughout 12 weeks, ranging from 94.3-96.1% which was very much higher than the study by Zaghloul et al3 (adherence of isotretinoin: 71.4%). Although it was not mentioned the isotretinoin dosage used in Zaghloul's study, in our study, we used a lower dose of isotretinoin (10 mg or 20 mg once a day), which could lead to better tolerability compared to the standard recommendation dosages (0.5 mg/kg/day). Other reason for good oral adherence in our cohort could be the simplicity and convenience of taking oral medication once daily. Moreover, those on oral treatment generally had moderate-severe acne. Hence, they were more concerned about their self-images and were more disciplined when in treatment.

We also assessed the patient's adherence to acne treatment using the ECOB questionnaire. Contrasting to the objective results, our patients had poorer adherence to oral therapy than topical treatment in both the groups. This finding could be due to question 3 in the ECOB questionnaire (oral treatment). If subjects had forgotten to take these drugs at any time during treatment, they would be considered non-adherers. Most of our participants had missed medication at least 1 day throughout the 12-week study, and thus they were regarded as poor adherers.

On the other hand, the ECOB questionnaire (topical treatment) question 3 asks if the subject ever stopped taking topical drugs because they thought it would do more harm than good. Though our participants also did miss topical medication throughout the period, the reasons given were not due to the harmful effects of the topical drug. Hence, they were considered as good adherers.

Disease severity and Reasons for Non-adherence

Non-adherence to treatment is one of the primary roots of treatment failure, poor clinical outcomes and intensified healthcare utilisation. Most of our cohort reported forgetfulness and a busy lifestyle as the main reasons they did not adhere to their medications. Multiple ways to increase patient treatment adherence include reminder systems via automated text messaging, phone calls, phone applications or internet-based surveys, simplifying the treatment regimen, education and more frequent clinic visits.[18] We aim to increase our patients' knowledge of acne and its treatment, as poor knowledge is one of the most frequently reported reasons for poor treatment adherence.[2,4] Our intervention group had better adherence to topical treatment and showed more significant disease improvement at week 12 than their counterparts. Several studies in atopic eczema and psoriasis also reported that patient education effectively improves the disease severity.[19-22]

Patient education acts as an adjunct in the management of dermatological disorders. Adequate patient education helps patients to understand their disease and manage treatment expectations better, as well as empowers them to take accountability for their health.[23,24] Topical treatment is the cornerstone of dermatological conditions. It acts directly on the affected area with minimal systemic effects. However, the application can be messy and time-consuming. As a result, patients often consider topical treatments minor, less effective, and therefore do not use them regularly. Some even say they would rather receive an oral drug or injection than topical drugs.[25]

Factors Affecting Non-adherence

We only identified patients in the intervention group, and those who believed the prescribed medication was effective had better adherence than their counterparts. We did not find other factors such as gender, age of onset, educational level, marital status, family history of acne, smoking status, type of acne, disease severity, knowledge about acne and patients' satisfaction associated with adherence. Our findings contrast with other authors who found that those with more severe acne, good patient satisfaction and knowledge of acne treatment positively affect compliance.[2,4] A possible explanation is that our subjects' number was much smaller than theirs, thus unable to elicit the association.

Medical Education and Counselling in Acne

Previously, a structured teaching program conducted in a secondary school in India has improved adolescent students' knowledge of acne.[26] Burleigh et al.[27] also demonstrated that acne education enhances adolescents' quality of life. Given the substantial amount of time spent in a school setting, we can incorporate acne education programs in high school teaching modules to provide teenagers with scientific and independent information to help with this common condition and its psychological effects.

LIMITATION

As acne condition improves with treatment and time, the amount of topical medicine required would change over time. Hence, we might overestimate the patient's required amount and project a much lower adherence rate among those on topical therapy. In general, the 12-weeks study duration might be too short to accurately assess the treatment response. Future study with longer study duration would be more ideal in this context. Besides that, the sample size calculation should also include differences expected from ECOB questionnaire outcome.

CONCLUSION

Patients have better adherence to topical medicine with effective disease education and treatment counselling. However, it did not improve adherence to oral medication. Better medication adherence hastens the improvement in disease severity.

ACKNOWLEDGEMENTS

We thank the Director General of Health Malaysia for his permission to publish this article.

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ORIGINAL ARTICLE

Feasibility and safety of transvaginal specimen extraction for laparoscopic living donor nephrectomy: an Indonesian perspective compared with three different approaches

Ahmad Zulfan Hendri, MD, Indrawarman Soerohardjo, MD, Khaerani Arista Dewi, MD, Aria Danurdoro, MD

Division of Urology, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Indonesia

ABSTRACT

Introduction: Laparoscopic live donor nephrectomy (LLDN) continues to expand in minimally invasive surgery; nevertheless, the studies are inadequate to compare standard kidney extraction with TV-NOSE in less-developed countries. This study compared TV-NOSE with conventional kidney specimen extractions.

Objective: To examine the feasibility of TV-NOSE in live donor nephrectomy.

Materials and Methods: 53 patients received LDN surgery at our hospital from September 2017 to December 2021. Retrospectively, living donor nephrectomy with TV-NOSE was compared to three different surgical procedures with standard specimen extraction.

Results: 53 donor patients were included: 15 open (OLDN), 12 retroperitoneoscopic living donor nephrectomy (RPLDN), 10 transperitoneal living donor nephrectomy (TPLDN), and 16 standard laparoscopic living donor nephrectomy with transvaginal extraction (SLLDN TV-NOSE). SLLDN TV-NOSE's longer operating time (p<0.0041) did not affect graft function. SLLDN TV-NOSE and RPLDN had shorter lengths of stay and better VAS trends than open LDN and TPLDN (p<0.05). SLLDN TV-NOSE donors reported acceptable surgical outcomes and unchanged sexual function. All patients had similar discharge creatinine levels, with 1-year transplant survival of 98% and just 1 graft loss in the TPLDN group.

Conclusion: SLLDN TV-NOSE is equivalent to RPLDN and better than open LDN and TPLDN in terms of duration of stay, VAS score, surgical outcomes, and sexual function. TV-NOSE is a safe surgical procedure with an acceptable donor complication. TV-NOSE may be safely conducted in both developed and developing countries with proper patient selection.

KEYWORDS:
Laparoscopic Nephrectomy; NOSE; Transvaginal; Laparoscopic live donor nephrectomy (LLDN)

INTRODUCTION

Compared with open surgery, laparoscopic surgery has many superiorities and has become the standard for nephrectomy donors. Laparoscopic surgery reduces the risk of early postoperative wound complications and long-term incisional hernia.[1] The smaller incision of the laparoscopic technique also reduces the length of hospital stay and the patient's recovery period.[2] However, traditional laparoscopic donor nephrectomy usually requires an additional large abdominal incision to remove the kidney. The additional incision increases the risk of abdominal wound complications and impairs postoperative recovery.[3] It also causes significant postoperative pain and cosmetic problems.[4]

Natural orifice specimen extraction (NOSE) allows laparoscopic donor nephrectomy to be performed through a standard trocar hole in the abdominal wall without additional incisions or extensions. Vaginal, gastral, rectal and bladder routes can be used for NOSE. However, for laparoscopic donor nephrectomy, transvaginal extraction seems to be the only suitable method.[5]

NOSE surgery for specimen extractions in living donors has been deployed previously in countries with more developed medical care systems, such as the Spain, Turkey and India.[6] However, because this method only requires some basic endoscopic instruments, NOSE can be applied in many health facilities worldwide, even in a resource-poor setting. Since January 2019, our institution has optimised TV-NOSE's application in our kidney transplant program, becoming the first hospital in Indonesia to adopt this new technology. The trial was initially conducted on 18 patients in Indonesia. It has become essential to critically assess its safety and efficacy against the well-established procedures of other previous laparoscopic living donor nephrectomy (LLDN). Thus, we retrospectively analysed the results of our first consecutive TV-NOSE with other previous laparoscopic approaches to donor nephrectomy and compared the outcome of our initial experience. The objective of this study was to describe the safety and feasibility of TV-NOSE during LLDN, especially in Indonesia. In addition, this study will mark a significant milestone for kidney transplantation surgery in Indonesia.

MATERIALS AND METHODS

Patient Population

In this study, we retrospectively examined the medical records of living kidney donors. This study was conducted in accordance with the local ethical committee and was approved by the Institutional Review Board of our University

This article was accepted: 07 March 2023
Corresponding Author: Aria Danurdoro
Email: danurdoroaria@gmail.com

(Ref. No: KE/FK/0594/EC/2022). Between September 2017 and December 2021, 53 kidney donor surgeries were performed by a surgeon in our hospital. All donor patients were hospitalised in the period of January 2017 to December 2018 underwent open surgery, and continued with laparoscopy transperitoneally with conventional specimen extraction (January 2019 to July 2019). By the August 2019, we started to perform TV-NOSE techniques for female donors and nephrectomy retroperitoneoscopically for male. We explained the procedure and received informed consent from all the patients. The study flow chart is shown in Figure 1.

In general, our institution's inclusion criteria for nephrectomy donor were institutional board approved considering its medical, ethical, legal and social aspects in live voluntary kidney donors, both in related and unrelated live voluntary kidney donors. The additional inclusion criteria for Standard Laparoscopic Living Donor Nephrectomy with Transvaginal-Natural Orifice Specimen Extraction (SLLDN TV-NOSE) used in our study were:

1. Patients are voluntarily willing to donate their kidney, hoping for minimal abdominal scarring;
2. The age range was determined based on previous literature where the minimum age was around marital age and no maximum age was imposed;[7–10]
3. Already given birth to a child; and
4. Patients having elastic and suitable diameter (7 cm) of vagina proven by gynaecologic exams.

We assessed the objective parameters including the patient demographics (gender, age, height, body mass index [BMI]), perioperative data (length of procedure, estimated blood loss and warm ischemic time [WIT]), postoperative data (length of hospital stay and visual analogue score [VAS]) and complications related to surgery (peri- and post-operatively). Donors were evaluated periodically after the surgery during the first 1 month, 3 months, 6 months, 1 year, and annually thereafter. The receiver of the kidney was also evaluated, especially for peri- and postoperative complications, graft function and post-implantation creatinine trends. Graft loss was defined as the loss of kidney function that occurred anytime post-transplantation due to either irreversible graft damage necessitating a return to dialysis, retransplantation (graft failure), graft removal, or recipient death with a functional kidney (patient death).[11] Acute rejection was defined as either biopsy-confirmed rejection or given antirejection therapy without a biopsy.[11]

The Female Sexual Function Index (FSFI) was collected from all patients who had undergone SLLDN TV-NOSE to evaluate the effect of transvaginal surgery on their sexual function, recorded 1 week before surgery and 3 months after the surgery. This tool is the most widely used to effectively measure the domains of sexual response according to criteria of both the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and the 1st International Consensus Conference Guidelines on female sexual dysfunction. This tool consists of a 19-item questionnaire, with the FSFI full-scale score of 26.55 as the best cut-off score for distinguishing between women with and without sexual dysfunction.[12] We also collected the postoperative Surgical Satisfaction Questionnaire (SSQ-8) modified for SLLDN TV-NOSE. This questionnaire requires patients to use the Likert scale (1 - very satisfied; 5 - very dissatisfied) to evaluate their SLLDN TV-NOSE surgical experience based on eight areas: pain control experience both in hospital and home care, their recovery to daily activities, returning to work, get back to exercise, the surgical results, the possibility of making the same treatment decision again, and their likelihood of recommending SLLDN TV-NOSE to other potential kidney donors.[13] The raw SSQ-8 data were then normalised to determine the SSQ-8 score by scaling from 0 to 100 according to the patient's level of satisfaction.

Pre-operative Preparations

According to guidelines issued by the American Society of Transplant Physicians,[14] all the donors underwent extensive medical and psychological evaluations. A thorough laboratory evaluation was performed for histocompatibility testing to ensure that healthy donors retain normal renal function after nephrectomy. Standard blood tests included the ABO histocompatibility, HLA cross-matching, complete blood count (CBC), serum chemistry (including liver function tests) and coagulation profiles. Donors were also screened for viral exposure, including hepatitis profile and exposure to human immunodeficiency virus, cytomegalovirus, varicella, and Epstein-Barr virus. Urinalysis, urine culture and 24-hour urine collection analysis were performed to assess the urine protein levels and creatinine clearance. Female patients with age >40 needed to have a recent negative Pap smear and negative mammogram. Radiographic assessments were performed using computed tomography (CT) angiography to obtain a preoperative mapping of the number and location of main and accessory renal vessels (if any) to obtain safe hilar anatomy and minimize the risk of vascular complications. Patients were advised to maintain a clear liquid diet during the day before surgery without preoperative bowel preparation. Prior informed consent was obtained for each surgical approach, including transvaginal kidney extraction. Vaginal speculum examination is performed only in SLLDN TV-NOSE donors to determine pelvic space adequacy, continued with vaginal douching preoperatively.

Intra-operative - Surgical Techniques

Standard Laparoscopic Living Donor Nephrectomy with Transvaginal-Natural Orifice Specimen Extraction

Under general anaesthesia, the donor is positioned in a right lateral decubitus position with modified lithotomy of the left leg to facilitate specimen extractions (Figure 2). Four laparoscopic ports were inserted: the first camera port was established at the apex of the umbilicus, two additional ports were established at the lateral upper and lower abdomen, one additional port was placed in the midline below the umbilicus and just above the pubic symphysis under direct vision (using all 11 mm ports or two 11 mm plus 5 mm ports) (Figure 3A). Under direct vision, a 12 mm trocar was inserted through the posterior fornix of the vagina. A vaginal tube (diameter 4.5 cm) was then placed in this entrance site to facilitate the specimen extractions. Dissection was performed according to standard laparoscopic transperitoneal nephrectomy. The ureter was cut, and the kidney was freed from the surrounding attachment. The Endo CatchTM pouch (Medtronic, Dublin, Ireland) was inserted through the

Table I: Demographic data of donors

Demographics	Surgery approach				*p* value
	SLLDN TV-NOSE (n = 16)	Open LDN (n = 15)	RPLDN (n =12)	TPLDN (n = 10)	
Age (year)	49.81	36.40	35.92	38.22	0.0007*
Gender (Male/Female)	0/16	11/4	11/1	9/1	0.8333*
BMI (kg/m^2)	24.87	25.72	24.17	23.42	0.5218*
ASA score, mean, range	1.563 (1-3)	1.400 (1 2)	1.308 (1-2)	1.444 (1 2)	0.7131*
Multiple renal arteries, n (%)	2 (12.5)	2 (13.3)	3 (25)	1 (10)	0.0014*
No complications after surgery, %	100	100	100	90	0.1150*

ASA indicates American Society of Anesthesiologists; BMI, body mass index; SLLDN TV-NOSE: Standard Laparoscopic Living Donor Nephrectomy with Transvaginal Natural Orifice Specimen Extraction; Open Living Donor Nephrectomy; TPLDN: Transperitoneal Laparoscopic Living Donor Nephrectomy; RPLDN: Retroperitoneoscopic Living Donor Nephrectomy; Open LDN: Open Living Donor Nephrectomy. Key: * – *p* value for Kruskal–Wallis test comparing four groups (SLLDN TV-NOSE versus Open LDN, RPLDN and TPLDN)

Table II: Intraoperative characteristics

	SLLDN TV-NOSE (n = 16)	Open LDN (n = 15)	RPLDN (n =12)	TPLDN (n = 10)	*p* value
Operating time, min (range)	216.3 (150 390)	154 (115-190)	173.8 (130 210)	197.5 (120 270)	0.0041*
Operative blood loss (mL)	175.6 (50 500)	182 (90 260)	175.0 (100 250)	215.5 (100 300)	0.4080*
Warm ischaemia time (s)	274 (120 450)	231 (111 502)	264 (126 732)	251 (121 507)	0.7226*
Bleeding requiring transfusion rate (%)	0	0	0	0	
Percentage of conversion rate to open surgery	0	N/A	0	0	
Intraoperative complications n (%)					
Vascular (aortic/lumbar vein/gonadal vein) injury	0	0	0	0	
Colonic/liver injury	0	0	0	0	
Splenic injury	0	0	0	0	
Pleural/lung injury requiring drainage	0	0	0	1 (10)	
Total	0	0	0	1 (10%)	<0.0001*
Postoperative complications					
Pulmonary	0	0	0	0	
Vascular	0	0	0	0	
Urological	0	0	0	0	
Wound infection	0	0	0	0	
Incisional hernia	0	0	0	0	
Chronic wound pain	0	0	0	0	
Total	0	0	0	0	N/A
Recipient complications, n (%)					
Overall ureteric complications	0	0	0	0	
Ureteric leak	1 (6.25%)	0	0	0	
Ureteric stricture	0	0	0	0	
Total	1 (6.25%)	0	0	0	<0.0001*

Key: * – *p* value for Kruskal–Wallis test comparing four groups (SLLDN TV-NOSE versus Open LDN, RPLDN and TPLDN)

Table III: Perioperative outcomes and graft function

	SLLDN TV-NOSE (n = 16)	Open LDN (n = 15)	RPLDN (n =12)	TPLDN (n = 10)	*p* value
Mean VAS score, mean (range)					
Day 1	2.1 (2 3)	3.7 (2-6)	2.1 (2 3)	2.2 (2 3)	<0.0001*
Day 2	1.3 (1 2)	2.5 (2-4)	1.25 (1 2)	1.8 (1 3)	<0.0001*
Day 3	0.68 (0 1)	1.6 (1-3)	0.75 (0 2)	1 (0-2)	0.0028*
Recipient discharge serum creatinine (mg/dL), mean (range)	1.3 (0.79 1.98)	2.1 (0.6-7.8)	1.8 (0.5 5.1)	1.7 (0.7 4.8)	0.6857*
Mean of donor postoperative hospital stay (days)	4.2 ± 1.18	6.1 ± 2.11	4.15 ± 1.14	5.6 ± 0.86	0.0025*
Acute rejection†, n (%)	0	2 (13.3)	0	2 (20)	<0.0001*
1 year graft survival‡ (%, death-censored)	100	93.3	100	100	<0.0001*

VAS indicates Visual Analog Scale; Key: † – Defined as either biopsy-confirmed rejection or given antirejection therapy without a biopsy. ‡ – Graft loss to determine the survival, was defined as the loss of kidney function that occurred anytime post-transplantation due to either irreversible graft damage necessitating a return to dialysis, retransplantation (graft failure), graft removal, or recipient death with a functional kidney (patient death). *– *p* value for Kruskal–Wallis test comparing four groups (SLLDN TV-NOSE versus Open LDN, RPLDN and TPLDN)

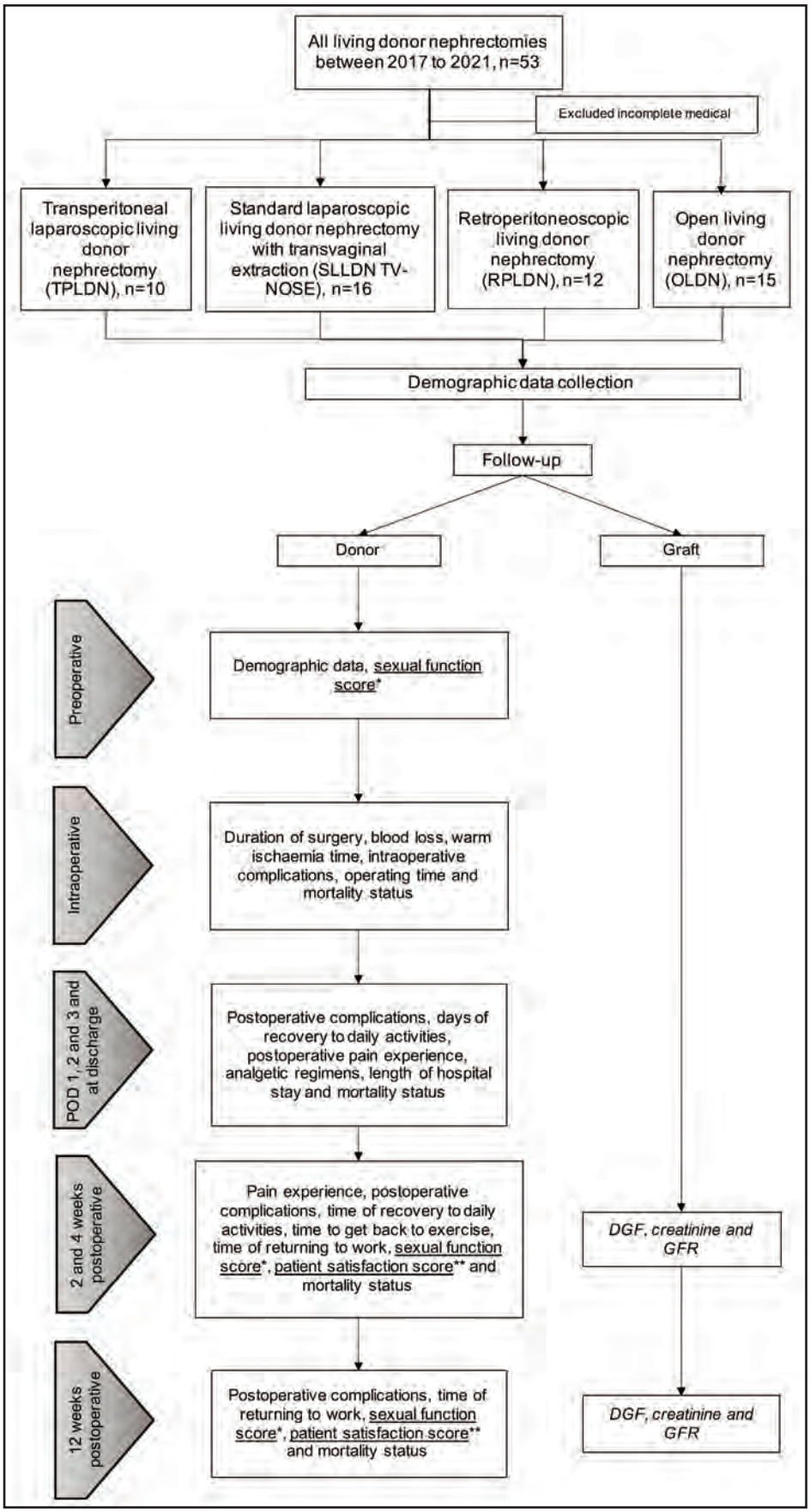

Fig. 1: Study design flow chart
Highlighted underlined texts: only performed in SLLDN TV-NOSE group; DGF delayed graft function; GFR glomerular filtration rate. *Assessed using the Surgical Satisfaction Questionnaire (SSQ-8) modified for SLLDN TV-NOSE. **Assessed using the Female Sexual Function Index (FSFI) score.

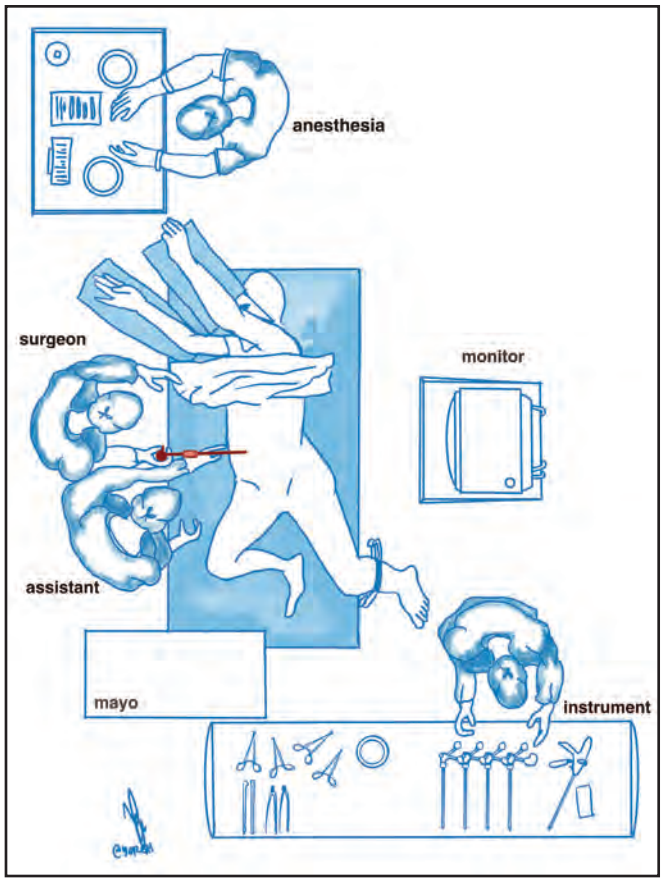

Fig. 2: Laparoscopic surgery personnel and operating room setup for Standard Laparoscopic Living Donor Nephrectomy with Transvaginal-Natural Orifice Specimen Extraction (SLLDN TV-NOSE) technique

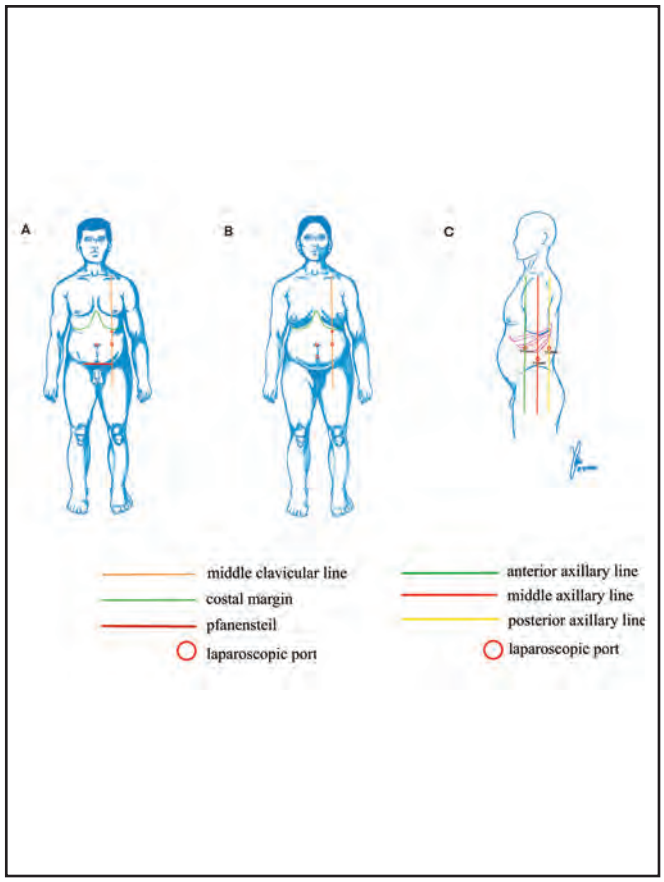

Fig. 3: Schematic laparoscopic ports access setup; (A) Standard Laparoscopic Living Donor Nephrectomy with Transvaginal-Natural Orifice Specimen Extraction (SLLDN TV-NOSE) technique; (B) Transperitoneal Laparoscopic Living Donor Nephrectomy (TPLDN); and (C) Retroperitoneoscopic Living Donor Nephrectomy (RPLDN)

vaginal tube. Preoperatively, we already made sure that the pouch is working properly and prepared to be completely open before vascular transection. The renal vessels were cut after double proximal clips' placement (Hem-o-lok, Teleflex, Wayne, PA, USA). The kidney specimen was extracted transvaginally using the Endo Catch™ pouch. The vaginal incision was sutured transvaginally under per speculum vision and interruptedly sutured through the entire thickness of the vaginal wall. A vaginal tampon was placed and maintained for 24 hours.

Transperitoneal Laparoscopic Living Donor Nephrectomy

Under general anaesthesia, the patient was positioned in lateral decubitus. The first camera port was established at the apex of the umbilicus. Three additional ports were established at lateral upper and lower abdomen under direct vision followed by insufflation of carbon dioxide up to 15 mm Hg (Figure 3B). The white line was opened, then the colon was moved towards the midline. On the left, the descending colon and spleen were assembled medially to improve the display of the whole kidney. A suprapubic transverse (Pfannenstiel) incision was made just before the vascular transection. After the dispensing access was ready, the renal vascular was clipped using the Hem-o-lok (Teleflex, Wayne, PA, USA). The kidney was then mobilised through the exit site. Abdominal wound closure was then performed.

Retroperitoneoscopic Living Donor Nephrectomy

Under general anaesthesia, the patient was placed in a lateral (right or left) lying position, with the operative bed was flexed to expand the space between the iliac crest and the costal margin. We made the small incision at the tip of the palpable 12th rib, and the retroperitoneal working space was developed using the modified balloon dilator inserted through this incision. Three 11 mm ports or two 11 mm and one 5 mm ports, were inserted. In some cases, an additional 5 mm port was inserted (Figure 3C). A Gibson incision was made just before the vascular transection. The Gerota's fascia was opened, and the kidney was dissected free from the surrounding tissue using a Harmonic Scalpel (Ethicon, Cincinnati, Ohio, USA) and LigaSure (Covidien, Boulder, CO, USA). The ureter was clipped and cut. The renal vessels were cut after being secured with a clip (Hem-o-lok, Teleflex, Wayne, PA, USA). The kidney was extracted through the Gibson incision.

Open Living Donor
The standard open donor nephrectomy was done through a flank incision with retroperitoneal access. The patient was placed in a full or half flank position. The incision was typically made at the intercostal between the 11th and 12th ribs and should not be longer than 12 cm. If necessary, it can be lengthened medially, as in the case of obese people. The renal artery was immediately ligated once it splits from the aorta. It was sewn or securely ligated across the remaining renal arterial trunk. The Satinsky clamp partially occluded the vena cava and the respective renal vein in the case of a suitably lengthy left or, more specifically, right renal vein. The vena cava was sown with non-resorbable sutures after the renal vein was transected. The muscle and fascia were carefully sewn layer by layer, and the skin incision was stitched intracutaneously.

Postoperative Care
Prophylactic drains were routinely maintained as least 24 hours postoperatively to ensure no post-operative complications such as active bleeding and to monitor the residual intraperitoneal fluid, but it should be removed no longer than 36 hours postoperatively to prevent surgical infection. We used epidural bupivacaine and an acetaminophen-based narcotic-free as the postoperative pain regimen. Most patients were discharged on the 4th day for laparoscopic donors. Vaginal packs were removed 24 hours postoperatively in SLLDN TV-NOSE donors.

Outcome Parameters
We collected data which may represent two main outcomes. The first was safety, indicated by blood-loss volume, WIT, surgery-related complications. The second was benefits or the efficacy, indicated by acute graft rejection and graft survival rate.

Statistical Analysis
Statistical analysis was done using SPSS version 13.0 (IBM Corp., Armonk, NY). One way ANOVA was performed on variables with parametric data. Kruskal Wallis test was used for those with non-parametric data. Post hoc analysis was performed using Bon Ferroni's test. The p-value of < 0.05 was considered statistically significant.

RESULTS

Patient Demographics
Demographic data of all subjects are shown in Table I. The total number of SLLDN TV-NOSE was 16. The other approaches included for comparison in this study were open (15 cases), retroperitoneoscopic (12 cases), and transperitoneal (10 cases). The mean age of SLLDN TV-NOSE was older than the other groups, and this was statistically significant (49.8 years vs. 36.4 years vs. 35.9 years vs. 38.2 years, p=0.0007). The baseline data of the donor's BMI and preoperative ASA score did not differ among the groups. The number of renal arteries was estimated by 3-dimensional CT. Of the 53 patients, eight of them had multiple arteries. The differences in the number of renal arteries were significant among the groups, with three patients in RPLDN, two patients in both SLLDN TV-NOSE and open groups, and only one patient in TPLDN group. Complication-free rate differences were not significant among the groups.

Intraoperative Donor Outcomes
The overall operating time was significantly longer (p<0.0041) in the SLLDN TV-NOSE group than in the other three groups (Table II). However, blood loss and WIT did not differ among the groups. The intraoperative complications rate did not differ among the groups, with one case of hemopneumothorax in the TPLDN group. No patients needed transfusion due to severe bleeding nor a surgical conversion from the laparoscopic surgery. There were no postoperative complications that required further surgical interventions. The length of postoperative hospital stay was significantly shorter in the SLLDN TV-NOSE and RPLDN groups (p=0.0025).

Perioperative Outcomes and Graft Function
VAS scores at postoperative days 1, 2, and 3 are shown in Table III, with significant differences, especially between the laparoscopic and open LDN groups. There was a trend towards better scores on the patient-reported VAS score in the SLLDN TV-NOSE and RPLDN groups compared to the TPLDN and Open LDN groups, with no significant differences between the first two groups. There were no cases of delayed graft dysfunction in this series.

The recipient discharge serum creatinine did not differ among groups. The acute rejection rate was 13.3% and 20% in the Open LDN and TPLDN groups, respectively. There was no acute rejection case in the SLLDN TV-NOSE and RPLDN groups. The overall 1 year graft survival of 98% (52 of 53 patients) was significantly different among the groups. The causes of graft loss were early patient death with a functioning graft for one case in the open LDN group.

Surgical satisfaction and sexual function in SLLDN TV-NOSE
The SSQ-8 modified for SLLDN TV-NOSE score postoperatively was 88.17. The pre- and post-operative FSFI score was 25.35 and 24.52, respectively. The FSFI score pre-and postoperatively did not significantly differ (p=0.52).

DISCUSSION

As part of the transplant surgery entity, nephrectomy for a living donor is considered one of the most demanding procedures because it is performed in a healthy individual rather than a sick patient.[15] Therefore, striving for the lowest potential morbidity without compromising graft function is mandatory.

The growing popularity of laparoscopic surgery throughout the world is making this technique begin to be widely used and become the current standard for nephrectomy donors. However, there are still several problems of traditional laparoscopic due to the requirement of the abdominal incision for specimen extraction. This increases the risk of complications of the abdominal wound and hinders post-operative recovery.[3] It also causes significant post-operative pain and aethetic problems.[4]

To counter the current problems and improve the surgical results, some surgeons have developed a new technique, the so-called NOSE surgery. This utilises an available natural orifice to facilitate specimen extraction from the body, thus

avoiding notable scars on the body's surface. Today, most NOSE procedures in urology use transvaginal routes, including nephrectomy donors. This can be explained by the following advantages[5]: (1) The risks of postoperative wound infection and leakage are lower due to less pathogenic bacteria and abundant blood supply in the vagina; (2) The vagina provides easy access to the peritoneal cavity, immediately entering the rectouterine pouch (pouch of Douglas) after accessing the posterior fornix; (3) The vaginal fornix mucosa has no somatic nerve sensation, thus minimising postoperative pain; (4) The vagina tissue has good flexibility and elasticity, which is suitable for the use of rigid instruments and beneficial during specimen extractions; (5) The vaginal incision can be done freely and safely, and then sutured under direct vision. Overall, patients may have benefited from superior psychological and cosmetic outcomes resulting in prompter recovery. It was in 2011 that the LLDN with transvaginal extraction was reported to be successfully accomplished.[6] Recently, this technique has been done in several other countries, such as Spain, Argentina, Italy, Turkey, and India. With the available literature, it is logical to assume that this technique can also be used in less developed regions because it only requires basic laparoendoscopic instruments.

Our study showed that comparing conventional laparoscopic and transvaginal extraction of nephrectomy donors has showed no significant difference in WIT and blood loss. Nevertheless, our WIT averaged 274 sec, which was longer than the other series, ranging from 165-220 sec.[7–9,16] A slightly longer period of warm ischemia is likely related to the early learning curve on laparoscopy but within limits that do not compromise the function of overall quality grafts, with a total ischemia time limit of 45 min.[17]

The SLLDN-TV NOSE has a slightly longer operating time than other groups, but the graft function showed no significant differences among the groups. Our initial experience showed that the mean operating time was 178 min. This was slightly longer than in the previous series by Kishore et al. (mean 155 min), Gurluler et al. (mean 156 min), and Karayagiz et al. (mean 150 min).[7–9] We assume the longer operating time is partly due to TV-NOSE surgery's single operator early learning curve. The SLLDN-TV NOSE was performed after the surgeon became more proficient in laparoscopic surgery and embarked upon further innovation. This procedure can be performed more effectively as the surgeon gets more proficient and gains more experience, as described by the improved duration of the last SLLDN-TV NOSE reaching statistical significance (first surgery vs. the 16th, 200 vs. 175 min [p=<0.0001]). Older age of the patient also strongly predicts the surgical difficulties and may affect the operating time in minimally invasive surgery, and this study showed significantly older age in the SLLDN-TV NOSE group than in the others.[18] Other factors such as BMI and gender can also potentially predict surgical difficulties, but we found homogeneity among the population in this study.

The recipient creatinine values were similar after periodic follow-up, showing no increasing value over time. Similar result was seen in a retrospective review which showed no significant difference in mean recipient creatinine level.[7,9,16]

The donor complications were relatively acceptable, shown by the no differences among the groups while ascertaining the safety of the extraction technique for kidney viability. These results were comparable to the other series.[7,9,16] Literature records, although rare, the complications that may occur have consisted of intraoperative colonic injury and bladder injury, and postoperative fever and bleeding requiring transfusions.[19,20]

Although the majority of open nephrectomy living donations are associated with shorter operative time and WIT, laparoscopic nephrectomy could be beneficial for patients through a shorter hospital stay, better aesthetics and a prompter return to work without affecting graft function.[2] Recent advancements also introduced the retroperitoneoscopic approach, which has advantages, particularly in patients who have undergone previous transabdominal surgery or have a high BMI. Nevertheless, in certain circumstances where instinctive positioning from anatomical landmarks and a larger workspace is needed, the transperitoneal approach remains favourable to most surgeons.[21] Our study shows that RPLDN is superior compared to open LDN and TPLDN in terms of shorter length of stay and post-operative pain experience.

We only performed the nephrectomy on the left kidney for every SLLDN-TV NOSE procedure. This is based on the earlier published meta-analysis implying that the left kidney has superior early outcomes, with lower rates of delayed graft function, technical failure, and graft thrombosis,[22] which was validated by another, more recent meta-analysis.[23]

Specifically for the use of the vagina as the extraction specimen route, several points are essential to thoroughly consider its viability prior to the surgery and overcome the potential intraoperative problems. Rigorous vaginal exams, usually performed by gynaecologists in our centre, were done to assess the vaginal elasticity and distensibility. The diameter of the vagina is standardised to a minimal 7 cm to facilitate convenient and safe specimen extraction. This is important to prevent any possible complications related to surgery in the future, such as uterine bleeding due to varicose vascular injury. Another critical point is to keep the vaginal trocar inserted in the midline during trocar insertion to avoid uterine vessel injury. Also, using a digital extension of the vaginal incision is considered safe and effective during specimen extraction, without increasing the risk of surrounding tissue injury and more bleeding with instrumentation tissue cutting. It is also essential to monitor any active bleeding after trocar removal. Lastly, the vaginal closure is to be sutured entangling the entire thickness of the vaginal wall to achieve homeostasis. By adhering to the components of this algorithm, we have standardised our approach to selecting the patients, optimised our transvaginal specimen extractions, and minimising the possible problems. To date, no significant challenges were encountered.

A previous study involving high populous kidney donors revealed that most kidney donors were female, which was found more in developing regions, including our study.[24] Most of the women had aesthetic interests concerning the post-

operative wound, which can be solved with minimally invasive surgery as in the NOSE technique. Most donors in our study were satisfied with the NOSE surgery, shown by a good SSQ-8 modified score. The utilisation of the vaginal route for specimen extractions may raise concerns about sexual function after the surgery. However, our study showed that the surgery did not affect the women's sexual function, with the FSFI score showing no significant differences pre-and postoperatively. These results proved that transvaginal extraction of kidney specimens was safe and acceptable among women donors.

This study has several limitations. First this cohort represents a small window to the learning curve data of a single surgeon, which may not be generalisable to others. However, a single surgeon's experience can be considered to minimise surgical confounders' bias. Second, the patient data were obtained retrospectively, and selection bias could impact the results. Third, we employed the nonmatched comparison among the study groups. We have tried to include patients with similar demographic profiles, however, the number of kidney donors in our centre is still limited.

CONCLUSION

This paper is the first to report our ongoing experience performing the Standard Laparoscopic Living Donor Nephrectomy With Transvaginal-Natural Orifice Specimen Extraction (SLLDN TV-NOSE) in Indonesia. This technique is evidently safe and feasible to be performed routinely in women living donors. It is also reproducible in developing regions as in our Indonesian centre. Despite taking longer operating time, the important perioperative variables and graft function are comparable between SLLDN TV-NOSE groups and conventional surgery. Promising results await in the future as the surgeon gains more proficiency and achieves a higher learning curve, in order to perform this technique more time-effectively. With the comparable graft function parameter and good postoperative satisfaction rate compared to conventional nephrectomy donors, SLLDN TV-NOSE can be considered as an excellent alternative to encourage more female donors. However, it is essential to select the patients carefully before surgery to minimise the complications. SLLDN TV-NOSE can not only be performed in developed countries with appropriate facilities but also in less-developed countries. Further studies are warranted to confirm our findings, since our data were collected retrospectively and only covered single-centre populations.

ACKNOWLEDGEMENT

The authors thank all surgical team and urology residents of Universitas Gadjah Mada who contributed to this study.

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Performance of the World Health Organization suspected COVID-19 case definition in cluster-associated and sporadic SARS-CoV-2 transmission in Malaysia

Sze Shyang Kho, MRCP[1,5], Aida Abdul Aziz, MMed (Rad)[2], Tonnii Loong Loong Sia, MRCP[1], Hema Yamini Ramarmuty, MRCP[3], Syazatul Syakirin Sirol Aflah, MRCP[4], Yasmin Mohamed Gani, MMed (UM)[2], Heng Gee Lee, MRCP[3], Chee Loon Leong, MMed (UM)[4], Zuhanis Abdul Hamid, MMed (Rad)[4], Felix Chua, FRCP[5]

[1]Hospital Umum Sarawak, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia, [2]Hospital Sungai Buloh, Ministry of Health Malaysia, Selangor, Malaysia, [3]Hospital Queen Elizabeth, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia, [4]Hospital Kuala Lumpur, Ministry of Health Malaysia, Kuala Lumpur, Malaysia, [5]The Royal Brompton Hospital, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom

ABSTRACT

Introduction: Cluster-associated transmission has contributed to the majority of COVID-19 cases in Malaysia. Although widely used, the performance of the World Health Organization (WHO) case definition for suspected COVID19 in environments with high numbers of such cases has not been reported.

Materials and Methods: All suspected cases of COVID-19 that self-presented to hospitals or were cluster screened from 1st April to 31st May 2020 were included. Positive SARS-CoV-2 rRT-PCR was used as the diagnostic reference for COVID-19.

Results: 540 individuals with suspected COVID-19 were recruited. Two-third of patients were identified through contact screening, while the rest presented sporadically. Overall COVID-19 positivity rate was 59.4% (321/540) which was higher in the cluster screened group (85.6% vs. 11.6%, p<0.001). Overall, cluster-screened COVID-19 cases were significantly younger, had fewer comorbidities and were less likely to be symptomatic than those present sporadically. Mortality was significantly lower in the cluster-screened COVID-19 cases (0.3% vs. 4.5%, p<0.05). A third of all chest radiographs in confirmed COVID-19 cases were abnormal, with consolidation, ground-glass opacities or both predominating in the peripheral lower zones. The WHO suspected case definition for COVID-19 accurately classified 35.4% of all COVID-19 patients, a rate not improved by the addition of baseline radiographic data. Misclassification rate was higher among the cluster-associated cases (80.6%) compared to sporadic cases (35.3%).

Conclusion: COVID-19 cases in Malaysia identified by active tracing of community cluster outbreaks had lower mortality rate. The WHO suspected COVID-19 performed poorly in this setting even when chest radiographic information was available, a finding that has implications for future spikes of the disease in countries with similar transmission characteristics.

KEYWORDS:
Cluster transmission, case definition, COVID-19, Malaysia, World Health Organization

INTRODUCTION

The rapid spread of COVID-19 from Wuhan, China, in the first two months of 2020 led to the declaration of its pandemic status on 11th March 2020.[1] In Malaysia, outbreaks occurring in clusters have significantly contributed to rising numbers of COVID-19. By June 2020, a total of 53 clusters had been identified, including 17 designated as active as of 28th June 2020.[2] By March 2021, a total of 1250 clusters had been notified to the Malaysian Ministry of Health, including 431 that were still classified as active.[3] In Singapore, 93% of new cases of COVID-19 reported in the first 4 months were linked to a known cluster.[4] In both countries, environmental settings implicated with rapid viral transmission included worker dormitories, schools, social events and mass religious gatherings.[5-9]

In this study, we prospectively evaluated the overall characteristics of suspected COVID-19 cases presenting to four large acute care hospitals in west and east Malaysia during the phase of rising incidence and spanned the peak of the outbreak in April and May 2020. All suspected COVID-19 cases were tested with SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (rRT-PCR), using that as a diagnostic reference. During the early phase of COVID-19 pandemic, the World Health Organization (WHO) released a case definition for suspected COVID-19 cases that focused on alert symptoms, particularly the presence of fever.[10] In contrast, our local case definition did not require fever as a compulsory symptom, which may have impacted case ascertainment and the identification of individuals with asymptomatic or mild diseases. We thus aim to assess the performance of the WHO case definition for suspected COVID-19 case ascertainment in our region. Since abnormalities on plain chest radiographs are known to accompany the presentation of COVID-19,[11] we further assessed the performance of the same case definition after

This article was accepted: 10 March 2023
Corresponding Author: Sze Shyang Kho
Email: bzk99@hotmail.com

incorporating baseline radiographic information. As a secondary aim, we also aim to evaluate the differences between cluster versus sporadically transmitted COVID-19 patients in Malaysia.

MATERIALS AND METHODS

Study Design and Setting

The regional acute care hospitals involved in this prospective observational cohort study were Hospital Kuala Lumpur (HKL) and Hospital Sungai Buloh (HSB) in West (mainland) Malaysia, and Hospital Umum Sarawak (HUS) as well as Hospital Queen Elizabeth Sabah (HQE) in East (Borneo) Malaysia. The study protocol was approved by the medical research and ethics committee, Ministry of Health Malaysia (NMRR-20-726-54589-IIR). The need for informed consent was waived in the interest of public health exceptionality.

Definitions

COVID-19 transmission has been classified by the WHO as cluster, sporadic or community-based.[12] A case cluster (also known as cluster outbreak) includes two or more epidemiologically but not necessarily residentially linked cases and who shared temporal, geographic and exposure factors with illness dates that occurred within an overlapping 14-day period.[7,12-15] In Malaysia, the term sporadic (or isolated) transmission was used to describe non-clustered cases that occurred locally or were imported, the latter not linked by association with locally transmitted cases. In March 2021, the WHO classified the principal mode of SARS-CoV-2 transmission in Malaysia in the first pandemic wave as cluster transmission.[12]

Strategy of COVID-19 Case Detection in Malaysia

COVID-19 contact tracing in Malaysia was undertaken by public health authorities through targeted or active screening of identified contacts of SARS-CoV-2-confirmed cases who presented to a hospital or community clinic with an acute respiratory illness.[16] In addition, and in line with the national COVID-19 strategy of "Search, Test, Isolate, Treat and Quarantine", comprehensive testing strategies targeting high-risk groups such as inhabitants of care homes, schools, labour contingents and returned travellers were implemented.[17] The nationwide COVID-19 response was coordinated by the National Crisis Preparedness and Response Center (CPRC). Tracing of close contacts and field investigations were undertaken by local district health officers.[16,18-19] Testing was widely performed and suspected COVID-19 cases identified through tracing, even if asymptomatic, were admitted to respective hospitals and quarantined until their rRT-PCR test result was available during the study period.[18-19]

Participants and Data Collection

All patients aged >12 years presenting with symptoms of an acute respiratory illness to each of the four sites or were identified from contact screening of suspected COVID-19 cluster outbreaks between 1st April 2020 and 31st May 2020 were included. In this study, we adhered to the national COVID-19 practice guidelines issued by the Malaysian Ministry of Health for the management of suspected and confirmed COVID-19 cases in the adult population.[20,21] Case-specific information including demographics, clinical information, laboratory results and plain chest radiographs were collected at the presentation. Routine blood investigations (full blood count with differential count, renal and liver function tests) were performed in all cases.[16,21] Coagulation profile, serum C-reactive protein, lactate dehydrogenase, ferritin and procalcitonin were only performed in symptomatic patients who required supplemental oxygen or higher respiratory support, subject to the availability of these tests at each study site.[16,21] D-dimer testing was not routinely available at all sites.

Confirmation of COVID-19 was defined by a positive rRT-PCR for SARS-CoV-2 viral nucleic acid in naso-pharyngeal swabs. Patients who tested negative remained designated as probable COVID-19 if their clinical presentation was compatible with the disease and no alternative cause was found to account for their symptoms. A non-COVID-19 diagnosis was ultimately concluded if further investigations revealed an alternative clinical explanation for the acute presentation. Patients with confirmed COVID-19 were stratified according to the location of care – medical ward or the intensive care unit (ICU) and method of transmission. Criteria for ICU admission included critical illness with multiorgan dysfunction, symptomatic or objective deterioration and/or increasing oxygen requirement over a 24-hour period despite ward measures.[20,21] All patients were followed until hospital discharge or death.

Acquisition and Scoring of Plain Chest Radiographs

Plain chest radiography was acquired as digital studies in the Emergency or the Radiology Department as part of standard clinical care. All radiographs were collated on a secure DICOM storage driver by a named site radiologist who conveyed the data to a centralised group of four study radiologists to be scored according to a template agreed a priori. The scoring team comprised an experienced thoracic radiologist (ZAH) and three senior thoracic radiology fellows who were blinded to the final clinical diagnosis and outcome.

The presence of radiographic ground-glass, consolidative, reticular and nodular opacities was recorded based on Fleischner society standard definitions.[22] Each hemithorax was divided into three horizontal zones bordered by the 4th and 8th ribs into upper, middle and lower zones; the number of zones affected (0–6) was recorded. The distribution of radiographic abnormalities was categorised by first dividing each hemithorax into three vertical zones; a central distribution was defined by involvement of the two most medial zones while a peripheral distribution was defined by involvement of the lateral third of either or both hemithoraces.

A week prior to commencement of the study, 50 randomly selected plain chest radiographs from COVID-19 patients were scored independently by members of the radiology panel. Moderate to good interobserver agreement was achieved for the presence of ground-glass opacity (κ=0.931, 95% CI 0.725-1.138), consolidation (κ=1.000, 95% CI 0.793-1.207) and reticulation (κ = 0.754, 95% CI 0.547-0.960). Good interobserver agreement was also observed for zonal involvement (κ = 0.751, 95% CI 0.643-0.858) as well as the distribution of abnormalities (κ=0.744, 95% CI 0.616-0.871).

Table I: Baseline clinical, laboratory and plain radiographic characteristic of confirmed COVID-19 cases stratified to a mode of transmission

		Overall N=321	Transmission		*p* value
			Cluster N=299	Sporadic N=22	
Clinical					
Age, median (IQR), years		34.0 (26.0-50.0)	33.0 (25.0-47.0)	50.0 (36.5-58.7)	<0.05
Gender, n (%)	Male	213 (66.4)	201 (67.2)	12 (54.5)	0.246
	Female	108 (33.6)	98 (32.8)	10 (45.5)	
Ethnicity, n (%)	Malay	180 (72.3)	174 (75.7)	6 (31.6)	<0.001
	Chinese	30 (12.0)	23 (10.0)	7 (36.8)	
	Indian	6 (2.4)	5 (2.2)	1 (5.3)	
	Native	33 (13.3)	28 (12.2)	5 (26.3)	
Current Smoker, n (%)		41 (13.4)	36 (12.7)	5 (22.7)	0.194
Presence of Co-morbidities, n (%)		70 (21.8)	58 (19.4)	12 (54.5)	<0.001
Co-morbidities, n (%)	Hypertension	49 (15.3)	42 (14.0)	7 (31.8)	<0.05
	Cardiovascular	11 (3.4)	9 (3.0)	2 (9.1)	0.130
	Diabetes mellitus	27 (8.4)	21 (7.0)	6 (27.3)	<0.05
	Malignancy	5 (1.6)	3 (1.0)	2 (9.1)	<0.05
	COPD	5 (1.6)	4 (1.3)	1 (4.5)	0.241
	Chronic kidney disease	7 (2.2)	6 (2.0)	1 (4.5)	0.431
Symptomatic, n (%)		122 (38.0)	105 (35.1)	17 (77.3)	<0.001
Symptoms	Fever	63 (19.6)	51 (17.1)	12 (54.5)	<0.001
	Cough	67 (20.9)	58 (19.4)	9 (40.9)	<0.05
	Sore throat	34 (10.6)	33 (11.0)	1 (4.5)	0.490
	Dyspnoea	22 (6.9)	16 (5.4)	6 (27.3)	<0.05
Temperature, median (IQR), °C		36.7 (36.5-37.0)	36.7 (36.5-37.0)	36.6 (36.4-36.9)	0.282
SpO_2, median (IQR), %		98.0 (97.0-99.0)	98.0 (97.0-99.0)	97.5 (96.0-99.0)	0.062
Heart rate, median (IQR), *beats/m*		86.0 (77/2-97.0)	86.0 (18.0-20.0)	90.0 (76.5-99.0)	0.383
Respiratory rate, median (IQR), *breathe/m*		20.0 (18.0-20.0)	20.0 (18.0-20.0)	20.0 (19.0-21.5)	0.069
Systolic blood pressure, median (IQR), mmHg		130.0 (121.0-140.0)	131.0 (122.0-140.0)	124.0 (114.0-142.0)	0.295
Laboratory					
Haemoglobin, median (IQR), g/dL		14.30 (13.10-15.40)	14.30 (13.20-15.40)	12.40 (11.30-15.05)	<0.05
Total white blood cell, median (IQR), × 10^9/L		8.00 (6.60-9.40)	8.00 (6.60 9.24)	8.00 (7.60-12.33)	<0.05
Absolute lymphocyte count, median (IQR), × 10^9/L		2.20 (1.70-2.78)	2.20 (1.78-2.79)	1.56 (0.88-2.79)	<0.05
Platelet, median (IQR), × 10^9/L		267 (222-311)	267 (222-314)	266 (198-294)	0.601
Blood urea nitrogen, median (IQR), *mmol/L*		3.80 (3.00-4.55)	3.70 (2.92-4.40)	4.60 (3.60-7.35)	<0.05
Alanine aminotransferase, median (IQR), *mmol/L*		25.0 (16.0-43.0)	25.0 (16.0-43.0)	32.0 (18.0-97.0)	0.294
C-reactive protein, median (IQR), *mg/dL*		0.40 (0.40-1.00)	0.40 (0.40-0.80)	6.00 (1.55-182.50)	<0.001
Radiographic					
Chest X-Ray Available, n (%)		316 (98.4)	295 (98.7)	21 (95.5)	0.241
Chest X-Ray Abnormal, n (%)		109 (34.5)	97 (32.9)	12 (57.1)	<0.05
Ground Glass Opacities, n (%)		90 (28.5)	80 (27.1)	10 (47.6)	<0.05
Consolidation, n (%)		34 (10.8)	29 (9.8)	5 (23.8)	<0.05
Reticulation, n (%)		29 (9.2)	23 (7.8)	6 (28.6)	<0.05
Bilaterality, n (%)		51 (16.1)	42 (14.2)	9 (42.9)	<0.05
Zone, n (%)	Upper	4 (3.7)	3 (3.1)	1 (9.1)	0.604
	Mid-Lower	80 (74.8)	72 (75.0)	8 (72.7)	
	No zonal predilection	23 (21.5)	21 (21.9)	2 (18.2)	
Distribution, n (%)	Central	27 (25.2)	26 (27.1)	1 (9.1)	0.179
	Peripheral	43 (40.2)	40 (41.7)	3 (27.3)	
	Mixed	28 (26.2)	23 (24.0)	5 (45.5)	
	Diffuse	9 (8.4)	7 (7.3)	2 (18.2)	
Outcomes					
ICU admission, n (%)		16 (5.0)	11 (3.7)	5 (22.7)	<0.001
Death, n (%)		2 (0.6)	1 (0.3)	1 (4.5)	<0.05

*Data are presented in median (IQR) and n (%). ICU = Intensive care unit.

Table II: Chest radiographic profile of confirmed COVID-19 patients stratified to ICU admission (n=316)

		Non-ICU Admission	ICU Admission	*p* value
Number of cases available for analysis, n (%), N=321		300 (98.3)	16 (100.0)	-
Abnormal CXR, n (%), N=316		93 (31.0)	16 (100.0)	<0.001
Ground Glass Opacities, n (%), N=109		76 (81.7)	14 (87.5)	0.574
Consolidation, n (%), N=109	19 (20.4)	14 (87.5)	<0.001	
Reticulation, n (%), N=109	16 (17.2)	12 (75.0)	<0.001	
Bilateral Changes, n (%), N=109		36 (38.7)	15 (93.8)	<0.001
Zone, n (%), N=107	Upper	4 (4.4)	0 (0.0)	<0.05
	Mid-Lower	73 (80.2)	7 (43.8)	
	No Zonal Predilection	14 (15.4)	9 (56.2)	
Distribution, n (%), N=107	Central	26 (28.6)	1 (6.2)	<0.001
	Peripheral	42 (46.1)	1 (6.2)	
	Mixed	17 (18.7)	11 (68.8)	
	Diffuse	6 (6.6)	3 (18.8)	
Total Zonal Involvement, median (IQR), N=109		2.0 (1.0-2.5)	4.0 (3.2-5.0)	<0.001

*Data are presented in median (IQR) and n (%). N is the total number of patients with available data. p-values were calculated by Kruskall Wallis Test, X2 test or Fisher's exact test as appropriate. CXR = chest radiograph, ICU = Intensive care unit

Table III: Performance of WHO suspected COVID-19 case definition with or without abnormal baseline plain chest radiograph (n=540)

	rRT-PCR Positive Rate, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Diagnostic Accuracy, % (95% CI)
Overall (N=540)						
Fulfilled WHO Criteria	59.4 (55.1-63.6)	11.8 (8.5-15.9)	69.8 (63.3-75.8)	36.5 (28.6-45.2)	35.1 (32.9-37.3)	35.4 (32.9-43.9)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	61.12 (56.7-65.3)	38.3 (32.9-43.9)	28.8 (22.7-35.6)	45.8 (41.7-49.9)	22.9 (19.1-27.3)	34.6 (30.5-38.9)
Cluster-associated Transmission (N=350)						
Fulfilled WHO Criteria	85.4 (81.2-88.9)	10.0 (6.8-14.0)	74.5 (60.3-85.6)	69.7 (56.3-80.4)	12.3 (10.7-14.2)	19.4 (15.4-23.9)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	85.2 (81.0-88.8)	36.2 (30.7-42.0)	58.8 (44.1-72.4)	83.5 (78.0-87.9)	13.7 (11.1-16.9)	39.6 (34.4-44.9)
Sporadic Transmission (N=190)						
Fulfilled WHO Criteria	11.5 (7.4-17.0)	36.3 (17.2-59.3)	68.4 (60.8-75.3)	13.1 (7.6-21.5)	89.1 (85.4-91.9)	64.7 (57.4-71.5)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	12.2 (7.7-18.1)	66.6 (43.0-85.4)	18.6 (12.7-25.8)	10.2 (7.7-13.5)	80.0 (66.7-88.8)	24.5 (18.3-31.7)

CXR = Chest radiograph, rRT-PCR = real time reverse transcriptase polymerase chain reaction, WHO = World Health Organization

Statistical Analysis

Data analysis was performed using SPSS, version 21 (Chicago, IL, USA). Normality of distribution was assessed by the Shapiro–Wilk test. Categorical data were expressed as frequency (percentage), with significance determined by the Pearson Chi-square or Fisher's exact test. Continuous parametric variables were expressed as mean (standard deviation) or median (interquartile range, IQR), with differences analysed by the independent t-test or Mann–Whitney U test. Interobserver agreement in relation to chest radiographic findings was evaluated by Fleiss' kappa coefficient. Sensitivity, specificity, positive predictive and negative predictive values were calculated using standard definitions via 2 × 2 contingency tables using SARS-CoV-2 rRT-PCR as the reference standard for COVID-19 diagnosis. Diagnostic accuracy was defined by the proportion of patients correctly classified by the screening criteria. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

A total of 540 individuals were recruited during the 8.5-week study period, comprising those who presented acutely to the study hospitals with symptoms suggestive of COVID-19 (190; 35.2%) and those who were contact-traced from cluster outbreaks of COVID-19 (350; 64.8%). The positive SARS-CoV-2 rRT-PCR test rate of the whole cohort was 59.4% (321/540). The remaining 40.6% (219/540) who tested negative included 19 cases ultimately labelled as probable COVID-19 due to COVID-19-compatible symptoms and 200 non-COVID-19 cases where an alternative diagnosis was identified to explain their clinical presentation.

The median age of the study cohort was 40 (IQR 28-58) with male gender accounting for almost two-thirds (63.1%) of all cases. The baseline demographic, clinical and radiographic characteristics of the cohort are summarised in Table I.

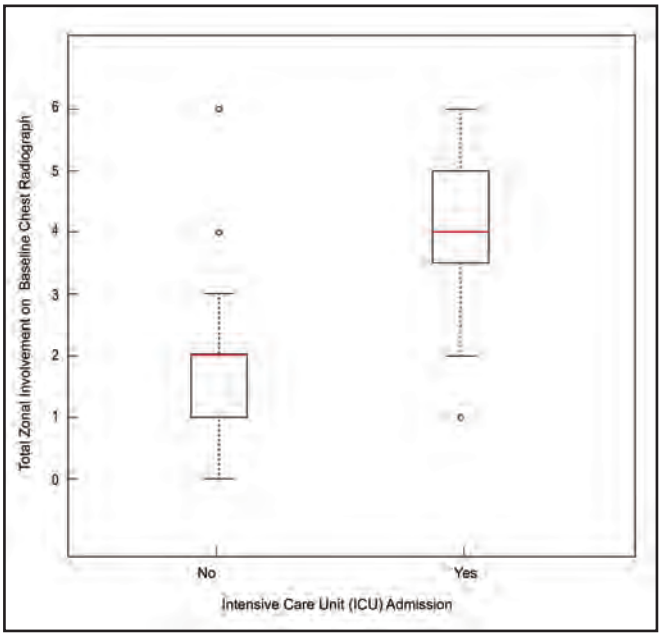

Fig. 1: Box and whisker plot demonstrating total zonal involvement on COVID-19's baseline chest radiograph in patients managed in medical ward versus patients requiring intensive care unit admission.

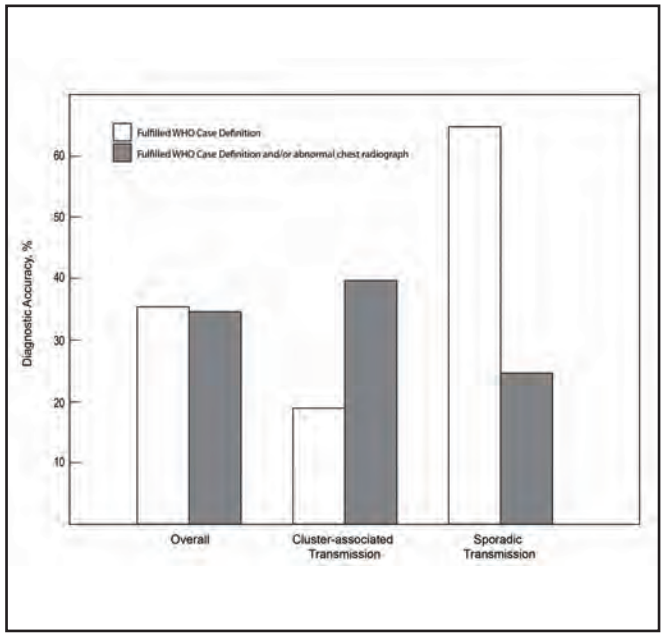

Fig. 2: Performance of WHO suspected COVID-19 case definition with or without abnormal baseline chest radiograph in overall, cluster-associated and sporadic transmission cohort.

Differences Between Sporadically Transmitted and Cluster-Associated COVID-19 Cases

93.1% (299/321) of cases that tested positive for SARS-CoV-2 were identified through the investigation of cluster outbreaks compared to only 6.9% occurring as sporadic COVID-19 cases with no epidemiologic link to a cluster. As most of the cluster outbreaks occurred in the Klang Valley urban conurbation around the capital Kuala Lumpur, the majority of COVID-19-positive patients recruited at HKL (86.2%; 43/50) and HSB (96.2%; 200/208) were identified through cluster contact tracing.[2]

COVID-19 patients detected through the screening of clusters were significantly younger (33 [IQR 25-47] vs. 50 [IQR 36-58], $p<0.05$), had significantly fewer comorbidities (19.4% vs. 54.5%, $p<0.001$) and were less likely to be symptomatic (35.1%; 105/299 vs. 77.3%; 17/22; $p<0.001$). The baseline vital indices (temperature, saturation, respiratory rate and systolic blood pressure) did not differ among the cluster or sporadic transmission groups. Malay ethnicity was associated with a higher proportion of COVID-19 cases from the cluster-screened group than non-Malay ethnicities (75.7%; 174/299 vs. 54.5%; 6/22, $p<0.001$). Hypertension, the commonest reported co-morbidity was more prevalent in the sporadic transmission group (14.0% and 31.8% respectively, $p<0.05$), as well as diabetes mellitus and underlying malignancy ($p<0.05$ for both).

The majority (95%) of patients with COVID-19 received ward-based care. 5% (16/321) of these patients were transferred to the ICU after a median of 6 (IQR 3.2-9.5) days on the medical ward; of these, 62.5% (10/16) were intubated and received invasive mechanical ventilation. Overall, the mortality rate for confirmed COVID-19 cases was very low at 0.6%, significantly lower still in the cluster-screened compared to sporadically transmitted cases (0.3% vs. 4.5%, $p<0.05$). These findings are summarised in Table I.

Baseline Radiographic Findings in Confirmed COVID-19 Cases

95.7% (517/540) of the whole study cohort underwent baseline chest radiography. Of the patients who tested positive for SARS-CoV-2, 98.4% (316/321) had a baseline chest radiograph. Just over a third of these were abnormal (34.5%; 109/316). In contrast, nearly two-thirds (62.2%) of patients who tested negative for SARS-CoV-2 had a baseline radiograph that was reported as abnormal.

Among the confirmed COVID-19 cases, the commonest radiographic abnormalities, present in isolation or in combination, were ground-glass opacity (28.5%, 90/316) and consolidation (10.8%, 34/316). These changes were evident bilaterally in 16.1% of cases and predominated in the middle and lower zones (Table I). Other radiographic findings are listed in Supplementary Table S6. COVID-19 patients who presented sporadically were more likely to have abnormal chest radiograph at baseline (57.1% vs. 32.9%, $p<0.05$) with nearly half of the patients (42.9%) presenting with bilateral radiographic changes with more diffuse distribution.

Abnormalities on the baseline radiographs of COVID-19 patients who subsequently required ICU admission were more likely to be distributed diffusely or to show mixed central and peripheral opacities without clear zonal demarcation (68.8% vs 18.7%, $p<0.001$). As a result, total zonal involvement quantified as a median value was higher in the ICU subgroup (4 [IQR 3.2-5.0] vs. 2 [IQR 1.0-2.5], $p<0.001$) (Figure 1 and Table II).

Performance of the WHO Clinical Definition for Suspected COVID-19

Approximately 1 in 5 (104/540; 19.2%) of the entire study cohort met the WHO clinical definition for suspected COVID-19. This definition was met by a significantly higher proportion of cases that had no links to a cluster outbreak (32.1%; 61/190) than those who were identified from clusters (12.3%; 43/350; $p<0.001$). Among the confirmed COVID-19 cases, only 11.8% (38/321) met the WHO case definition for suspected COVID-19.

Overall, the WHO clinical definition correctly classified only 35.4% of COVID-19 patients in our study cohort, with an overall sensitivity of 11.8% and positive predictive value of 36.5%. The addition of an abnormal baseline chest radiograph increased both parameters to 38.3% and 45.8%, respectively but was associated with decreased specificity. This change translated to an overall diagnostic accuracy of 34.6%, which was not different from employing the case definition alone with radiography.

Among cluster-associated cases, the WHO definition correctly identified only 19.4% of patients and misclassified the remaining 80.6%. The misclassification rate was reduced to 60.4% with the addition of a chest radiograph obtained at the presentation. In contrast, 64.7% of the self-presenting (non-cluster associated) cases were correctly classified by the same definition, although the addition of radiographic information reduced this classification accuracy to 24.5% (Figure 2). The details of the overall diagnostic performance with corresponding 95% confidence intervals are shown in Table III.

DISCUSSION

Our study, conducted across four major hospitals, provides an account of the characteristics of first-wave COVID-19 in Malaysia. The majority of individuals who tested positive for SARS-CoV-2 were identified by screening the contacts of index COVID-19 cases within epidemiologic clusters (groups of individuals aggregated by common geographic, temporal and exposure factors).[12] Our cohort therefore differs from reports of predominantly sporadic or isolated case transmission, with its distinctively lower median age, higher proportion of asymptomatic cases, fewer co-morbidities, infrequent radiographic abnormalities and low mortality.

The low COVID-19-associated case fatality rate in the present study is in line with the officially published first-wave death rate of 1.4% in Malaysia and comparable to the mortality rate of COVID-19 in neighbouring countries.[6,23-27] Patients in our study population presented with symptoms similar to those reported in high-incidence regions.[28-30] Descriptions of cluster outbreaks elsewhere have similarly highlighted a high number of mild cases with few deaths.[31] The reasons underpinning the low mortality in cluster transmissions are poorly understood; like patients who present sporadically and have no link to clusters, such cases are managed according to their clinical status and were not pre-emptively given corticosteroids or other treatments. However, younger age, a common characteristic amongst cluster-linked cases, has been associated with a lower likelihood of acquiring SARS-CoV-2 infection and reduced susceptibility to the severe clinical manifestations of COVID-19.[32,33] There is also a broad acknowledgement that children do not develop COVID-19 as readily as adults and those of older age run the highest risk of a fatal outcome.[26,30,32,34]

Ethnicity has emerged as an important risk factor for COVID-19 globally. The reasons why Malay ethnicity was associated with a higher proportion of COVID-19 cases from the cluster-screened group in our analysis are unclear; however, the prevalence of Malay ethnicity in the current study closely reflected the background ethnic distribution in Malaysia.[35] A higher frequency of Malay ethnicity has also been reported in patients with severe COVID-19 in Malaysia, including those who were admitted to the ICU.[27] A higher risk of acquiring the infection amongst the Malay population may potentially be linked to a greater proportion of multigenerational families, more frequent social congregation within common domiciliary areas and the smaller size of dwellings in Malay-populated semi-urban locations. A higher diagnostic rate of COVID-19 may also have resulted from a number of well-publicised large outbreaks of COVID-19 linked to mass religious gatherings during the first wave of COVID-19 pandemic in Malaysia.[5]

Descriptions of the plain radiographic presentation of COVID-19 in South-East Asia are few. A recent study reported that COVID-19 patients with bilateral and predominantly upper and middle zone abnormalities were more likely to require supplementary oxygen.[36] In the present study, only a third of the baseline chest radiographs were abnormal, lower than the 50–69% frequency of radiographic abnormalities reported by others.[37-40] This disparity likely reflects differences in cohort constitution such as the higher rate of acute symptomatic COVID-19 cases in studies that did not involve active contact tracing. Two of our main observations were consistent with the experience of others, namely that COVID-19 pneumonia has a predilection for the peripheral lower zones and that patients who require ICU admission have more diffuse radiographic changes on admission.[36-40] Crucially, there was also considerable overlap in the radiographic findings between COVID-19 patients and individuals with alternative diagnoses in the population that we studied.

Application of the WHO case definition of suspected COVID-19 to our overall population resulted in the misclassification of 64.6% of cases, a rate that was not diminished by the addition of chest radiographic information. This phenomenon was likely related to the high prevalence of asymptomatic cases in this population as the WHO clinical case definition released during the early part of the SARS-CoV-2 outbreak emphasised 'alert' symptoms namely fever, cough or dyspnoea.[10] Amongst the non-cluster identified cases in our study, the WHO clinical criteria correctly identified 64.7% with COVID-19. However, its accuracy was paradoxically reduced by the addition of radiographic information due to the misdiagnosis of alternative conditions that presented with similar clinical and radiographic features. In effect, our observations reveal the limitations of the WHO case definition when applied to populations with sparse or non-specific symptomatology and who may not

reveal themselves to have been potentially exposed to SARS-CoV-2 within a case cluster at the time of presentation. They also show that plain chest radiography has low diagnostic sensitivity for COVID-19 when the rate of community transmission of SARS-CoV-2 is not high.

The following limitations are notable. The high proportion of cluster-screened cases may have biased our study towards a higher COVID-19 identification rate. However, our observations reflected the prevailing disease transmission situation in Malaysia at the time of the study. The cases presenting to HSB were enriched for SARS-CoV-2 positivity, given its role as the national infectious disease referral centre. Inclusion of two hospitals on the island of Borneo allowed us to include cross-sectional cohorts of suspected COVID-19 from two centres distant from the capital city. The lack of detailed epidemiologic information on the clusters from which some of our patients came precluded an in-depth analysis of the transmission chain. Similarly, we did not have information on viral clearance or clinical sequelae beyond the period of hospitalisation as the study was not designed to collect follow-up data. However, we note that the case fatality rate of COVID-19 in Malaysia has remained static since the completion of the study. The absence of a detailed acute blood work-up including D-dimer was due to the inconsistent availability of these assays across the study sites. Nonetheless, the clinico-radiographic features of COVID-19 patients in this study are similar to those reported from other countries. Finally, the true performance of the WHO suspected case definition may have been underestimated as the diagnosis of probable COVID-19 was based on a single rather than serial negative swab results. Repeat testing would have been ideal but it was not possible within the limitations of this study. Admittedly, the group of patients in question constituted a minority (3.5%) of the overall cohort.

CONCLUSION

In Malaysia, one consequence of the common occurrence of cluster outbreaks is the higher frequency of asymptomatic cases present within small geographic areas. Whether this observation helps explain the low case fatality rate in this country is unclear. Our findings show that the WHO case definition for identifying suspected COVID-19 performed poorly in this setting and support the view that large-scale viral testing, rigorous contact screening and strict containment measures, including movement control policies, remain key to efforts to control SARS-CoV-2 transmission.

ACKNOWLEDGEMENT

We thank the collaborators from all study sites and institute for clinical research Malaysia *(H.H. Chua, P.P. Goh, H.K. Ho, N.C. Huan, F.H. Husin, I. Ismail, J.H.L. Kong, K.S. Lau, S.L.S. Lui, S.R. Mohd Yakop, J.Y. Ong, M. Pathmanathan, Y.T. Saw, S.T. Tie, T.F. Wong, M.C. Yong)* who made this project a success. We are grateful for the support of the European Respiratory Society (Clinical Training Fellowship to SSK). We also thank the Director General of Health, Malaysia, for permission to publish this article.

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Firefighter satisfaction and happiness at work: how big is the effect?

Muthukumaran Mariapan, MD[1], Mohd Nadzrul Safiq Abd Rahim, MDBCh[1], Rosnah Ismail, DrPH[1], Nor Hisham Mohammad, MBA[2], Ashrul Riezal Asbar, BMEng[3], Ismail Abdul Ghani, Bachelor of Management with Honors[4]

[1]Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia, Selangor, Malaysia, [2]Headquarters, Fire and Rescue Department of Malaysia, Lebuh Wawasan, Presint 7, Putrajaya, Malaysia, [3]Planning and Research Division, Fire and Rescue Department of Malaysia, Nilai, Negeri Sembilan, Malaysia, [4]Fire and Rescue Department of Malaysia Negeri Pahang, Kuantan, Pahang, Malaysia

ABSTRACT

Introduction: Firefighter satisfaction plays a crucial role in overall workplace happiness. We seek to quantify the effect size of firefighters' satisfaction with happiness at work after adjusting for socio-demographic attributes.

Materials and Methods: This study used data from an online cross-sectional survey that was conducted from 24 June to 24 July 2021 in the Fire and Rescue Department of Malaysia. Firefighters were approached using the saturation sampling technique. They received online surveys via email through the Director of State and follow-up reminders through the Assistant Director of State Operations. A total of two filter questionnaires were employed i.e. type and duration of service. Firefighters stating that they were volunteer/auxiliary firefighters or had been in service for 2 years or less were excluded. In this study, data from 6041 out of 8581 firefighters were included for further analysis. The survey utilised the validated staff satisfaction index (SSI) and the happy career (HC) scale for in-service firefighters. SSI was a dual-dimension index consisting of welfare and protection against hazards at work, with 16 subdimensions. The HC is a five multi-dimensional items scale. Then, we used multiple linear regression to obtain the coefficient of determination while adjusting for age groups, gender, marital status, job grade, years of service and region of service.

Results: A total of 6041 eligible data points were analysed in the study. The mean (±SD) age was 38.70 (8.97) years, of which 95.9% were male. The firefighters were in service for a median of 14 years (Q1, Q3: 8, 21). The firefighter reported higher life satisfaction (mean [SD] = 78.30 [9.15]) than happiness at work (mean [SD] = 77.22 [0.20]). The mean happiness scores differed significantly between years of service groups (p<0.001), region of service (p<0.001), marital status (p=0.029) and grade (p<0.001). Firefighters' satisfaction contributed 42.7% of workplace happiness (βadj=1.096 [95% CI: 1.064, 1.128]; p<0.001) after adjusting for frontline, married, the central region of service and male gender as control variables.

Conclusion: Firefighter satisfaction had a large effect size on happiness at work (42.7%). However, the interpretation of this effect size should be done with caution because happiness at work is inseparable from other life dimensions such as stability in matrimonial relationships and finances, involvement in leisure and religious activities and being mentally healthy.

KEYWORDS:
Firefighters, satisfaction, happiness, workplace, effect size

INTRODUCTION

Satisfaction at work is the integrated set of psychological, physiological and environmental conditions that encourage employees to state that they are satisfied or happy with their jobs.[1] Happiness is a fundamental, transient positive emotion in human hedonic experience, which may largely be influenced by a job and juggling with other life domains such as stability in a matrimonial relationship and finances, involvement in leisure activities and religious community, and being mentally healthy.[2] Although job satisfaction and positive emotion while working are viewed as happiness-related constructs in the workplace, positive emotion while working and job satisfaction are not similar.[3] Often job satisfaction has a predominant focus on the cognitive evaluations of job features rather than feelings about the job or emotional experiences while working. A prior study has noted the importance of higher cognitive job function mediates emotional feelings for the intention to act efficaciously.[4] A study showed that firefighters who had positive emotion, i.e. meaning of work, positively related to in- and extra-role job performance.[5] Positive emotion such as being happy signifies that things are working as predicted,[6] a mediator between job demands and organisational outcomes[7] and boosting health.[8]

Previous studies on the job or employee satisfaction used generic assessment items that were not reflective of the nature of firefighting and the hazardous dynamic environments encountered. Firefighting is a high-risk job susceptible to physical and mental injuries from carrying out duties. In addition to hazards encountered at the scene of a fire, firefighters also perform search and rescue and respond to natural as well as man-made disasters. Approximately 23 to 25 firefighters are injured per 1,000 fires, while about seven injuries per 10,000 occur in non-fire emergencies.[9] Although organisational commitment may be an antecedent to

This article was accepted: 12 March 2023
Corresponding Author: Rosnah Ismail
Email: drrose@ppukm.ukm.edu.my

firefighters' health, wellness, and fitness, existing job resources for protecting firefighters against various hazards to prevent injury and disease as well as safeguarding their welfare should be evaluated promptly. Welfare is repeatedly mentioned as a factor able to magnetise firefighters' feelings of happiness as they conduct heroic actions.[10] It is worth studying how much welfare and protection against hazards affect firefighters as some factors including being married, serving in a less hectic region, and stepping up the career ladder have been mentioned as contributing to firefighters' happiness.

Although happiness at work is the main focal outcome in psychological studies compared to the occupational field,[10–12] happiness at work has reached the attention of the managerial level in the Fire and Rescue Department of Malaysia (FRDM). Firefighter satisfaction and its relation to workplace happiness were recently documented using customised Staff Satisfaction Index (SSI) and happy career (HC) scales. These scales represent promising tools to identify which areas of hazard protection and welfare issues are crucial to improving and enhancing satisfaction and happiness at work. This targeted outcome is parallel to a range of studies stating that some aspects of organisational practices and qualities (e.g. supervision, camaraderie with teammates about workload, security, career pathways and rewards) and how they are perceived by the organisation's members, consistently predicts happiness-related attitudes.[13,14] In this study, happiness at work was viewed as a firefighter's feelings of happiness related to their job regarding meaning, personality fit, work environment and skill utilisation.[15] We seek to quantify the effect size of firefighters' satisfaction with happiness at work after adjusting for socio-demographic attributes. It is hoped that managerial personnel can prioritise the demands of professional and personal lives for the betterment of planning.

MATERIALS AND METHODS

Study Design and Population

This study used data from an online cross-sectional survey that was conducted from 24 June to 24 July 2021 in the Fire and Rescue Department of Malaysia. Firefighters were approached using the saturation sampling technique. Saturation sampling is done where all the members on a particular e-list are invited to participate.[16] This technique minimises non-response bias and ensures that each person can respond only once. Firefighters received online surveys via e-mail through the Director of State and follow-up reminders through the Assistant Director of State Operations. They were filtered by two questionnaires, i.e. type and duration of service. Firefighters stating that they were volunteer/auxiliary firefighters or had been in service for 2 years or less were excluded. In this study, data from 6041 out of 8581 firefighters were included for the further analysis. The data surpassed the expected minimum sample size of 725. The sample size was calculated using G*Power 3.1.9.7 software. The 'a priori' sample size was calculated for the F test family with multiple linear regression (MLR) (fixed model, R2 deviation from zero) with the settings as follows: f^2 = 0.02 (small effect size), α=0.05, number of predictors = 7, and power set at 80%.

Study Tools

This study utilised a questionnaire packet consisting of socio-demographic information (i.e., age, marital status, gender, job grade, service region and duration of service), the SSI, and the happy career (HC) scale. The SSI and HC were newly developed and underwent a series of validation procedures, replicating previous suggestions[17] for assessing firefighter satisfaction and happiness levels at work. The SSI had dual dimensions, namely protection against hazards and welfare factors. The protection against hazards consisted of 10 subdimensions measuring engineering and administrative control as well as personal protective devices: (1) personal protective suit, PPS (five items, composite reliability [CR] value = 0.925), (2) workspace WORKSP (three items, CR value = 0.925), (3) facility and equipment, EQUIP (seven items, CR value = 0.934), (4) documentation related to standard operating procedures and work manuals, DOC (four items, CR value = 0.939), (5) addressing occupational safety and health issues, OSH (five items, CR value = 0.920), (6) workload, WORKLOAD (five items, CR value = 0.933), (7) psychological care, PSYCARE (six items, CR value = 0.933), (8) physical fitness, FITNESS (six items, CR value = 0.910), (9) health surveillance, HSURV (four items, CR value = 0.936) and (10) supervision, SV (three items, CR value = 0.923). The welfare factors consisted of six subdimensions measuring (1) salaries, SALARIES (four items, CR value = 0.928), (2) special allowances, SpALLOW (two items, CR value =0.828), (3) compensation for occupational injury or death, COMPENS (three items, CR value = 0.953), (4) career development, CAREER (four items, CR value = 0.917), (5) Care, CARE (five items CR value = 0.894) and (6) compassion, COMPASSION (four items, CR value = 0.858). All SSI items began 'I am satisfied with . . . '. A higher score indicates higher satisfaction.

The HC scale consists of five multidimensional items and was used to measure the firefighter's feelings of happiness related to their job regarding meaning, personality fit, work environment, and skill utilisation. A total of three HC items started with 'I am happy to work in the Department because . . .'. the other two items omitted the initial wording because they would have made them too lengthy, exceeding 15 words per statement. The firefighters were expected to rate their level of agreement with SSI and HC using a five-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = slightly agree, 4 = agree and 5 = strongly agree). There was no undecided or neutral response. The firefighters were forced to evaluate their level of agreement rather than sitting on the fence. A higher score indicates higher happiness at work.

In confirmatory factor analysis (CFA), the SSI was regressed on the HC scale using partial least squares structural equation modelling, namely the reflective formative disjoint two-stage approach. The analysis revealed that SSI and HC satisfied all measurements and structural model assessments. Protection against hazards at work (β=0.370, p<0.001) and safeguarding welfare (β=0.375, p<0.001) explained 46.6% of the happiness variance. Both dimensions displayed small to medium effect sizes and relevance to predicting happiness (Q^2=0.339). Details can be accessed via previous publications.[18]

Table I: Socio-demographic profile of respondents

Profile	Frequency	Percent
Gender		
Male	5794	95.9
Female	247	4.1
Marital Status		
Single	669	11.1
Married	5257	87.0
Widowed	115	1.9
Region of Service		
Northern	1286	21.3
Central	1993	33.0
Southern	1535	25.4
East Coast	880	14.6
East Malaysia	347	5.7
Job Grade		
KB19	3788	62.7
KB22/24/26/28	1670	27.6
KB29/32/38	426	7.1
KB41/44/48	134	2.2
KB52 and above	23	0.4
Education		
Postgraduate (Master/PhD)	74	1.2
Degree/ Professional Certificate	1637	27.1
Secondary	4317	71.5
Primary	13	0.2

Note: Northern – Perlis, Kedah, Penang and Perak; Central – Selangor, Kuala Lumpur and Putrajaya; Southern – Melaka, Negeri Sembilan and Johor; East Cost – Terengganu, Kelantan, Pahang; East Malaysia – Sabah, Sarawak dan Labuan

Table II: Descriptive data for firefighter satisfaction and happiness at work (n = 6041)

Variables	Score	Mean ± SD	95%CI for mean
Firefighter satisfaction	0 to 100	78.30 ± 0.12	78.07, 78.53
Protection Against Hazards			
Personal Protective Suit	5 to 25	18.11 ± 0.05	18.02, 18.19
Workspace	3 to 15	11.03 ± 0.03	10.98, 11.08
Equipment	7 to 35	23.51 ± 0.07	23.38, 23.64
Documentation	4 to 20	13.05 ± 0.03	14.99, 15.11
OSH	5 to 25	19.10 ± 0.04	19.03, 19.17
Workload	5 to 25	17.65 ± 0.04	17.57, 17.74
Psychological Care	6 to 30	21.33 ± 0.05	21.34, 21.54
Fitness	6 to 30	21.13 ± 0.05	22.05, 22.23
Health Surveillance	4 to 20	14.37 ± 0.04	14.29, 14.46
Supervisor	3 to 15	11.92 ± 0.02	11.88, 11.97
Staff Welfare			
Salary	4 to 20	11.86 ± 0.05	11.77, 11.96
Special Allowance	2 to 10	7.75 ± 0.02	7.71, 7.79
Compensation	3 to 15	9.65 ± 0.03	9.58, 9.72
Career Development	4 to 20	16.18 ± 0.03	16.12, 16.24
Care	5 to 25	16.58 ± 0.05	16.48, 16.69
Compassion	4 to 20	16.29 ± 0.03	16.24, 16.35
Happiness at work	0 to 100	77.22 ± 0.20	76.83, 77.61

Note: OSH – addressing occupational safety and health.

Table III. Mean differences in firefighter satisfaction and happiness at work scores according to socio-demographic factors (n = 6041)

Socio-demographic	Firefighter satisfaction score							Happiness at work score					
	n	Mean	SD	95%CI for mean		Test	*p* value	Mean	SD	95%CI for mean		Test	*p* value
				LL	UL					LL	UL		
Age													
Less than 30 years	1379	79.01	9.88	78.49	79.53	F (3, 6037)	<0.001	76.55	16.47	75.68	77.42	F (3, 6037)	<0.001
31 to 40 years old	2205	77.48	9.42	77.09	77.87	= 13.67		76.55	15.98	75.89	77.22	= 6.97	
41 to 50 years old	1648	78.20	8.62	77.78	78.62			77.72	14.57	77.02	78.43		
More than 50 years	809	79.53	7.85	78.98	80.07			79.14	13.75	78.19	80.09		
Years of service													
Less than 10 years	2475	78.44	9.84	78.05	78.82	F (3, 6037)	0.006	76.34	16.42	75.69	76.98	F (3, 6037)	<0.001
11 to 20 years	2023	77.86	8.95	77.47	78.25	= 4.10		77.52	15.13	76.86	78.18	= 6.73	
21 to 30 years	1331	78.46	8.27	78.02	78.91			77.90	14.21	77.14	78.66		
More than 30 years	212	79.91	7.70	78.87	80.95			80.37	14.08	78.46	82.27		
Gender													
Male	5794	78.32	9.15	78.08	78.55	t = 0.71	0.483	77.33	15.46	76.93	77.73	t =2.75	0.006
Female	247	77.90	9.10	76.76	79.04			74.59	15.31	72.68	76.51		
Marital status													
Single	669	79.59	10.19	78.81	80.36	F (2, 6038)	<0.001	75.81	16.67	74.55	77.08	F (2, 6038)	0.029
Married	5257	78.15	8.99	77.91	78.39	= 7.63		77.42	15.31	77.01	77.84	= 3.54	
Once Married	115	77.64	9.46	75.90	79.39			76.07	14.75	73.34	78.79		
Job Grade													
KB19	3788	78.21	9.44	77.91	78.51	F (4, 6036)	0.479	76.35	15.68	75.85	76.85	F (4, 6036)	<0.001
KB22/24/26/28	1670	78.29	8.46	77.89	78.70	= 0.87		78.21	14.77	77.50	78.92	= 10.96	
KB29/32/38	426	78.80	9.33	77.91	79.69			79.30	15.69	77.81	80.79		
KB41/44/48	134	79.19	8.31	77.77	80.61			81.27	15.18	78.68	83.87		
KB52 and more	23	79.72	9.97	75.41	84.03			86.23	13.26	80.50	91.96		
Region													
Northern	1286	77.54	8.89	77.05	78.02	F (4, 6036)	0.001	76.64	15.43	75.80	77.49	F (4, 6036)	<0.001
Central	1993	78.14	9.64	77.71	78.56	= 4.59		76.30	15.97	75.60	77.00	= 7.69	
Southern	1535	78.90	8.96	78.45	79.34			78.13	15.27	77.36	78.89		
East Coast	880	78.48	8.37	77.93	79.04			77.21	14.02	76.29	78.14		
East Malaysia	347	78.97	9.74	77.94	80.00			80.60	16.36	78.87	82.32		

Table IV Predictors for happiness at work among firefighters (n = 6041)

Variables	Simple linear regression			Multiple linear regression				
	Coefficients β	95% CI for β		Adjusted Coefficients β	95% CI for β		t	Sig.
		LL	UL		LL	UL		
Constant				−11.197	−14.276	−8.117	−7.128	<0.001
Firefighter satisfaction	1.095	1.062	1.127	1.096	1.064	1.128	66.521	<0.001
Frontline	−2.331	−3.135	−1.526	−1.729	−2.352	−1.107	−5.446	<0.001
Married	1.571	0.411	2.731	2.229	1.331	3.126	4.868	<0.001
Serve in central region	−1.369	−2.198	−0.540	−0.903	−1.532	−0.273	−2.811	0.005
Male	2.736	0.767	4.705	2.120	0.627	3.613	2.784	0.005
Tertiary education	−0.084	−0.950	0.781	–	–	–	–	–
Service 10 years and more	1.491	0.699	2.283	–	–	–	–	–

Note: Forward method (r2 = 0.427; the model fits reasonably well; model assumptions are met; no multi-collinearity problem detected)

Analysis

SSI Scoring

As the maximum score for the satisfaction index is 100%, we derived the index score based on the weighted value of each dimension from CFA (Figure 1). The mathematical formula for the score involved three steps.

Step 1. Score formula for dimension protection against hazards.

$$\frac{\begin{array}{c}(0.422 * SV) + (0.323 * OSH) + (0.109 * DOC) + \\ (0.199 * FITNESS) + (0.022 * HSURV) + \\ (0.081 * WORKLOAD) + (0.124 * PPS) + \\ (0.012 * PSYCARE) - (0.201 * EQUIP) + (0.127*WORKSP)\end{array}}{\mathbf{23.35}} \mathbf{X\ 100\%}$$

Step 2. Score formula for the welfare factor dimension.

$$\frac{\begin{array}{c}(0.567 * COMPASSION) + (0.326 * CAREER) + \\ (0.134 * CARE) + (0.143 * SpALLOW) + \\ (0.089 * SALARY) + (0.079 * COMPENS)\end{array}}{\mathbf{24.94}} \mathbf{X\ 100\%}$$

Step 3. Total score for the staff satisfaction index.

50% of score protection against hazards + **50% of score welfare factor**

Workplace Happiness Scoring

In that the five items in HC are multidimensional, the interval score was generated via the Rasch measurement model[19] using the following formula:

USCALE = (wanted range)/(current range),

UMEAN = (wanted low) - (current low x USCALE).

Descriptive, Bivariable and Multivariable Analyses

The collected data were checked for missing values. The online Excel data was submitted in the IBM Statistical Package for Social Science (SPSS) version 26 for data normality and summarisation. A one-way analysis of variance (ANOVA) was used to determine whether there were any statistically significant differences between the means of three or more independent groups, for example, age, years of service, marital status, job grade, and region of service. Pearson correlation coefficients, r, were calculated for firefighter satisfaction and happiness at work. The value of r <0.2 – very weak, 0.2 to <0.4 – weak, 0.to <0.6 – moderate, 0.6 to <0.8 – strong, and r ≥0.8 – very strong relationship.[20]

MLR was applied to quantify the effect size between the SSI score and the HC score relationship after controlling for frontline job scope, marital status, service in the central region, male gender, education level and years of service. The effect size was determined by the coefficient of determination, R^2, which is a statistical measure in a regression model that determines the proportion of variance in the dependent variable that can be explained by the independent variable. The R^2 categories for the linear regression were <0.02 very weak, 0.02 to <0.13 weak, 0.13 to <0.26 moderate, and 0.26 and above indicated a substantial effect size.[21] Some socio-demographic variables were regrouped into dichotomous categories as the following: (1) Job grade of KB19 was grouped as frontline whilst grade KB 22 and above was grouped as non-frontline, (2) marital status was grouped as married and single/once married, (3) those reported working in Selangor, Kuala Lumpur and Putrajaya were grouped as the central region of service whilst those reported working in other states were grouped as non-central region, (4) those reported had completed college, university or any form of professional certification were grouped as tertiary whilst those reported had secondary school and below were grouped as non-tertiary and (5) service year was grouped as less than 10 years and 10 years and more.

The MLR replicated analysis steps as described and statistical assumptions were checked.[22] A forward method was chosen to get the parsimonious model. A scatter plot was created between the HC and SSI scores to ensure a linear relationship. Variables with a p value up to 0.5 in the simple linear regression were selected if they supported plausibility. Once the preliminary model was obtained, the interaction term between independent variables was checked followed by multicollinearity checking. The independence of residuals was checked using the Durbin–Watson statistic at a range of 0 to 4. Outliers were checked using casewise diagnostics followed by the determination of normality assumptions of the residues.

Ethical Considerations

This study was approved by the Research Ethics Committee on 8 December 2020. Project code FF-2020-490.

RESULTS

Socio-Demographic Profile

A total of 8581 firefighters responded. Only 6041 eligible in-service firefighters who rendered their service across the nation for at least two years were selected. The mean (±SD) age was 38.70 (8.97) years (range: 22 to 61 years). About one-third of the respondents were over 40. The majority of the respondents were male (95.9%), married (87%), had education until secondary school (71.7%), and served in a non-central region of Malaysia (67%; Table I).

Firefighter Satisfaction and Happiness at Work

Subdimensions of firefighter satisfaction were generally found to be scored above three per item except for salary (Table II). The majority of the firefighters agreed that they had supportive supervision at work (97%), department compliance with occupational safety and health requirements (95.6%), department provided necessary standard operating procedures, standards of guidelines and manuals (94.4%), physical fitness-related matters (90.6%), career development (97.5%), satisfaction with the special allowance provided (94.6%) and the level of compassion showed by the management and department (98%). Although higher firefighter satisfaction was strongly related to high happiness at work (r=0.65, p<0.001), only 70.1% and 41.2% of the surveyed firefighters reported satisfaction and happiness of more than 75%, respectively.

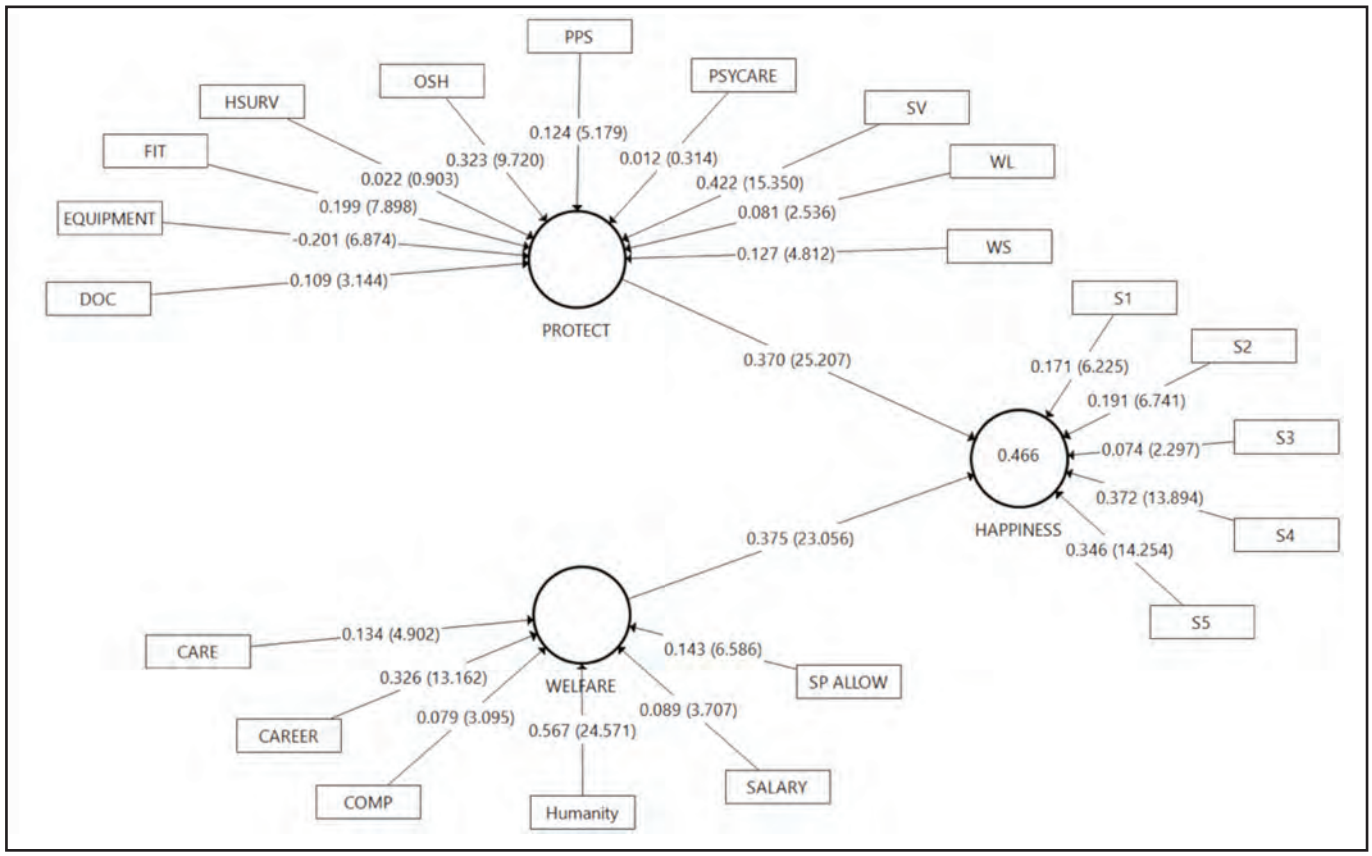

Fig. 1: Staff Satisfaction Index on Happiness Scale: A Reflective-formative disjoint two-stage approach

The mean total satisfaction score of 78.30 (9.15) was higher than the mean total happiness score, of 77.22 (15.46), for all firefighters. The mean total happiness score differed significantly for all socio-demographic attributes. It varies in age groups (p<0.001), years of service (p<0.001), gender (p=0.006), marital status (p=0.029), job grade (p<0.001) and region of service (p<0.001). The highest happiness levels were reported by grade KB52 and above (86.23 ± 13.26), followed by KB41/44/48, KB29/32/38, KB22/24/26/28 and KB19 in descending order. Firefighters who served more than 30 years or serve in East Malaysia reported happiness of more than 80%, i.e. 80.37 ± 14.08 and 80.60 ± 16.36, respectively (Table III).

This study found that firefighter satisfaction is a significant factor in predicting happiness at work (β_{adj} = 1.096 (95% CI: 1.064, 1.128); p<0.001) after adjusting for frontline job scope, male gender, the central region of service and married status. Satisfaction alone contributed to 42.7% of the overall happiness level (Table IV).

DISCUSSION

This study aimed to quantify the effect size of satisfaction with happiness at work after adjusting for socio-demographic attributes among in-service firefighters. Firefighter satisfaction and its relation to workplace happiness were recently surveyed using customised tools, namely the SSI and HC scales. In this gender-representative sample, our analysis provides a contemporary benchmark of satisfaction's effect size. Firefighters are worth to be studied because their professions are high-risk in nature and unpredictable, with intermittent periods of intense physical and psychological stress. They are expected to execute all 14 essential tasks against the types and levels of emergency services provided to the local community.[23] Responding to sudden emerging incidents, and performing a series of emergency tasks to protect the public from incident-related hazards and possible risks inherent to it necessitates constant physical readiness at any time with the optimum level of protection against various hazards.

We found firefighters' happiness at work is largely driven by job satisfaction regarding protection against hazards and ensuring welfare factors (42.7%). This result is because firefighters, on average, were satisfied with the positive work state created by the FRDM in protecting their men against various hazards at work and safeguarding their welfare. This finding corroborates the ideas of Pasca and Wagner[24], who suggested that a positive work state is negatively related to satisfaction and positively related to psychological symptomatology. FRDM creates a positive work state by complying with the hierarchy of control measures at all stages of deployment. Firefighters are equipped with suitable modernised engineering control technology, administrative application at various stages of deployment, and appropriate personal protection equipment (PPE) specification. In addition, FRDM also provides a peaceful mind of securing the welfare matters of the deployed firefighters in any case of injury and death.

The modernised technology of engineering controls builds in what firefighters need to reduce the risk of hazards and increase safety parameters to assure the risk associated with the essential tasks is worth taking. For example, the HAZMAT vehicle is designed to be resilient against toxic fumes of on-site hazardous material. Thermal imaging is used to detect infrared energy emitted by people, objects and materials to facilitate firefighters in search and rescue, and non-contact laser thermometers are used to monitor the risk of a boiling liquid expanding vapor explosion (BLEVE). In addition, the design of passive fire protection and the installation of active fire protection systems (25) enable firefighters to go into a building for fire suppression and come out alive. A failure in these systems whether mechanical in nature of an active fire protection system or a breach of passive fire protection could lead to unsafe conditions and firefighter injury or death. Therefore, the engineering control requires regular checks and maintenance to ensure it remains in favour over administrative and personal protective equipment.

Administrative controls application such as standard operating procedures, compliance inspections, industrial code of practice and best practices guide how firefighters manage their own risk of hazards. Risk management is a process initiated by identifying what risks are inherent in fire suppression, rescue activities and managing hazardous material, followed by a risk assessment and analysis. Risks are assessed in terms of how often and how bad the consequences could be. Thus, risk control can be chosen appropriately using engineering controls and administrative and personal protection equipment to minimise the risks. Firefighters undergo regular training and simulations to equip them with this knowledge and inculcate relevant skills so that it becomes their second nature to do automated series of actions in responding to real case scenarios. In addition, training and simulations also allow firefighters to test PPE suitability and integrity during pre-operations. Three major issues about PPE can be highlighted, e.g. suitability concerning the variation of human factors, dexterity, and mobility challenges due to oversizing and integrity of protection in the interface between protective equipment and full gear.[26] These issues are important as it may negatively effecting firefighters' work efficiency and safety in a hazardous environment.

In any standard textbook of occupational health, PPE is the last hierarchy of control measures,[27] albeit the most critical lifeline to firefighters in an emergency. If the administrative and engineering controls are adequate, the need for PPE lessens yet matches the inherent hazards. Generally, PPE is provided for major tasking to protect against thermal threats and toxic gas inhalation during fire suppression and to protect against physical injuries (e.g., cuts, punctures, slips, trips, and falls) during rescue operations. During fire suppression, firefighters are equipped with heavy, fire-resistant full gear including a breathing apparatus. In other dangerous rescue situations, such as crashed vehicles, structural collapses and industrial accidents, or high-angle rescue, firefighters require different sets and types of equipment to protect them against hazards during cutting, breaking, shoring, searching, and lifting. Those PPE sets are at par or above specifications with optimum cost efficiency to enhance task-related abilities to cope with task-specific demands. The specialised PPE must undergo regular field testing to ensure it fits for performance, which is affected by a wearer's body physique. Those with skinny body types might experience back strain, which triggers rapid fatigue or fall injuries due to the shifting of the body mass centre while carrying a heavy self-contained breathing apparatus on their back. Therefore, the physical fitness of the wearer is another element that must be surveyed.

In the world of firefighters, there are eight definitive standards of firefighter physical fitness[28] that firefighters should be able to maintain throughout their career to make them safe before saving others. The eight definitive sets of physical fitness measures include (i) optimising core strength, (ii) cardiovascular capacity, and (iii) flexibility, as well as muscular strength, endurance, and power for (iv) pulling, (v) pushing, (vi) carrying, (vii) lifting and (viii) dragging functional movements. All elements of physical fitness are important for shaping the body's physique to keep performing under strenuous activity for lengthy periods[29] while wearing or carrying heavy full gear or equipment. In Malaysia, this physical fitness is assessed by the standard individual physical proficiency test (IPPT) at every 6 months.[30] The IPPT consists of (i) a 2.4-km run to test cardiovascular capacity, (ii) a bent-knee sit-up to test endurance of the abdominal core and hip flexor muscles, (iii) a standing broad jump to test explosive muscular power of the lower body, (iv) pull-up (for males)/inclined pull-up (females) to test upper-body muscular strength and endurance, and (v) 4 × 10-m shuttle run to test the speed of movements, agility, and coordination.

Of all the physical standards, the 2.4-km run to test cardiovascular capacity is mandatory. If the firefighter fails the run, the other IPPT components also fail. As a firefighter, optimum cardiovascular capacity is a weapon to maintain job performance for a long time without being lethargic. Cardiovascular capacity concerns the transportation of oxygen to working muscles for effective energy production and the efficiency of this muscle exchange and oxygen use.[28] Firefighters are required to have a minimum aerobic capacity of 42 ml/kg/min[23] to tolerate various types of physical activities while wearing a self-contained breathing apparatus. Based on contemporary values, aerobic capacity ranges from 37.45 to 58.21 ml/kg/min for responding to various incidents, for instance, interventions in traffic accidents, extinguishing fires, incidents with hazardous materials, rescues and forest fires.[28,31]

Safeguarding welfare is another positive element that magnetises firefighters' feelings of happiness at work. A possible explanation for this might be that well-guarded welfare while on duty is a good motivator of work meaning i.e. dimension of happiness at work.[15] This hypothetical explanation accords with earlier observation,[5] which showed that work meaning played an important role in firefighter's work engagement level. Firefighters are engaged to focus on the task and absorbed with the strategies and tactics to accomplish missions. The engagement is rather non-emotional and unconscious at the moment, leading to firefighters' positive psychology.[32] Examples of positive

psychology leading to happiness at work include feelings of confidence, bravery and sincerity.[33] The dimension of special allowance as part of welfare factors also contributed to happiness at work because it was perceived as a reward for their specialised hard work.[34] Special allowance is given to subject-matter experts or specialised teams such as special tactical operation and rescue (STORM), hazardous materials (HAZMAT) and multi-skilled teams (MUST). The other dimensions such as compensation for injury, permanent disability and death, career development, caring and compassion provide peace of mind while deployed. As expected, the salary dimension was recorded as the lowest mean score in the welfare dimension. This is because salary and some allowances set by another public entity may need a lengthier time for passing any monetary increment demands. Although the salary is not an attractive incentive, many young adults try their luck to be recruited because they perceive firefighting as a prestigious job locally[35] and internationally.[36]

Firefighting is perceived as a prestigious job because it provides the opportunity to serve the local community among people with specific types of traits in a manner greater than themselves. Generally, firefighters have complementary personality traits. The frequently observed personality traits of those who are attracted to the fire services are extroversion and conscientiousness.[39,38] Extroversion means they feel excited by external stimuli such as interacting with people or receiving calls to thrilling emergencies and scenarios.[39] The conscientiousness trait is positively correlated with psychological skills.[38] These personality traits can predict an individual's habitual way of reacting to work-related challenges and stressors. Those traits explain why firefighters are systematic, dependable and generally plan matters even in adrenaline-fuelled situations. Harmonising between these inner selves and daily living by the nature of the fire service leads to happiness.[40]

However, our study found that firefighters reported high satisfaction scores and low happiness at work, similar to previous findings.[41] These findings further support the idea that they remain resilient while suppressing their own emotions.[14] There are always chances of line-of-duty death while saving the public from incident/disaster and willing to make the ultimate sacrifice, if necessary. In a prolonged emergency, they look out for the interests of others before theirs. Sometimes firefighters experience the loss of close buddy in an incident. Certainly, they want to survive in this prestigious career with their courage, wellness, health and sanity intact. This is because the majority of firefighters cannot simply walk away and pursue another inviting dream job.

This is the first study describing the effect size of firefighters' satisfaction on happiness at work recorded among a gender-representative sample of firefighters nationwide in Malaysia. This work offers a comprehensive depiction of the relationship between firefighter satisfaction and happiness consistent with the culturally adapted measures of firefighters' interest. Therefore, the results of the current study provide valuable data that reinforces the 16 factors of minimising hazards and ensuring welfare as antecedents for being happy at work. Moreover, areas for continual improvement specifically identified the prevention of essential tasks effects during service years for example equipment for essential tasks and administrative controls. Although the current study was observational, the generalisation of the effect size to the hypothesised model yields a meaningful value. Hence, SSI and HC are promising tools for annual monitoring at the FRDM level in safeguarding satisfaction and happiness among their men.

Happiness at work has not been able to separate from the other life dimensions such as matrimonial relationships, stability in finances, involvement in leisure activities and religious community, and being mentally healthy. These life dimensions should be measured as adjusted predictors in future studies. In the future longitudinal study, it is worth conducting happiness at work as a specific mediating factor between satisfaction and safety job performance among firefighters in Malaysia.

This online survey was not feasible for accessing the entire firefighters. The survey was limited to those with formal email and internet access as well as the swiftness of email distributions from top management (KB41/44/48 or KB52) to operation crews (KB19) who resided at various fire stations throughout Malaysia. In addition, computer literacy to respond to online surveys may be a significant challenge for older firefighters. However, this inherent coverage bias is considered a minor disadvantage because Table I showed that the sample was representative of gender and job grade. However, generalisation of the data to other volunteer/auxiliary firefighters should be done cautiously.

CONCLUSION

Firefighter satisfaction had a large effect size on happiness at work (42.7%). Enhancing protection against hazards and ensuring welfare factors are critical, as they empower firefighters to carry out their essential tasks against the types and levels of emergency services provided to the local community safely and soundly. However, the interpretation of this effect size should be done with caution because happiness at work is inseparable from other life dimensions such as stability in matrimonial relationships and finances, involvement in leisure and religious activities, and being mentally healthy.

AUTHOR CONTRIBUTIONS

ARA and RI contributed to the conception and design of the study. MM and MNA organised the data and conducted the statistical analyses as well as the preliminary discussion. MM, MNA, and RI drafted sections of the manuscript. NHM and IAG were the key informants and provided experiential learning for RI. All the authors engaged in revising, reading, and approving the submitted version of the manuscript.

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ORIGINAL ARTICLE

Discipline as complete mediation in the implementation of the *Theory Planned Behaviour* of nurse's handwashing compliance

Kumoro Asto Lenggono, PhD[1], Qomariyatus Sholihah, PhD[2], Gatot Ciptadi, PhD[3], Sri Andarini, PhD[4], Ahsan, PhD[5], Dion Kunto Adi Patria, MN[6], Sapto Adi, PhD[7]

[1]Department of Environmental Studies, Post Graduate School Brawijaya University, Malang, Indonesia, [2]Department of Industrial Engineering, Faculty of Engineering, University of Brawijaya, Malang, Indonesia, [3]Departement of Animal Production and Institut Biosains University of Brawijaya, Faculty of Animal Husbandry, University of Brawijaya, Malang, Indonesia, [4]Department of Public Health, Faculty of Medicine, University of Brawijaya, Malang, Indonesia, [5]Department of Nursing, Faculty of Health Science, University of Brawijaya, Malang, Indonesia, [6]Department of Nursing, Institute of Science and Health dr. Soepraoen, Malang, Indonesia, [7]Department of Sport Science, Faculty of Sport Science, University of Malang, Malang, Indonesia

ABSTRACT

Introduction: Hospital-acquired infection is still one of the health problems in the world that require infection control and prevention efforts, especially nurses' hand washing compliance. Various strategies and efforts to improve handwashing compliance include educational approaches, motivation and improvement of the health care system, one of which is through the use of *The Theory Of Planned Behaviour* application in solving handwashing compliance.

Materials and Methods: Quantitative research with a survey approach and observation of hand washing compliance of all nurses N = 321 with a sample of n = 178 nurses. The research variables studied consisted of intention, discipline, self-assessment, opportunity compliance and implementation of the nurse's hand washing. Nurse handwashing compliance observations were made by Infection Prevention Control Link Nurse (IPCN) committee. Data analysis using structural equation modelling (SEM) with smart partial least square *(SmartPLS 3.0)* application.

Results: The nurse's intention to apply the theory of planned behaviour has no significant effect on the implementation of hand washing with path coefficients of 0.104 and p-value 0.221 > 0.05. The effect of nurses' intentions on the implementation of nurse hand washing through discipline is significant with a value of variance accounted for (VAF) 0.8043 or 80.43 % of nurse discipline is a complete mediation variable.

Conclusion: Discipline as a complete meditation variable in the application of the theory of planned behaviour in the compliance of nurses' hand washing five moments six steps. Nurses are expected to continuously improve their discipline independently or be assisted by training activities facilitated by the hospital.

KEYWORDS:
Intention, Discipline, Self-assessment, Hand washing, Five moments six steps

INTRODUCTION

Hand washing is the most important action in reducing the risk of transmitting microorganisms. Hand contact with blood, body fluids, secretions, excretions and contaminated patient equipment or items is an important indicator of infection prevention and control.[1,2] Nurses' handwashing behaviour in compliance with five moments six steps of hand washing still needs attention, considering that 19% are at risk of causing phlebitis incidents in infusions.[3] About 40% of the spread of germs on hands contributes to cross-infection from health workers.[4] In this case, the WHO has set global (world) efforts and challenges for patient safety through compliance with hand washing.[5]

The low level of nurse handwashing compliance is the basis for a multi-modal approach strategy through education, motivation and improvement of the service system in increasing nurse compliance in handwashing.[6] The theory of planned behaviour is a conceptual framework that aims to explain the determinants of certain behaviours. According to Ajzen[7], the central factor of individual behaviour is that behaviour is influenced by individual intentions (behaviour intention) towards that particular behaviour. The intention to behave is influenced by three components attitude, subjective norm and perceived behaviour control.[7] The development of research using the Theory Of Planned Behaviour application as an effort to identify the role of intention in increasing hand washing compliance has been proven to have a significant effect on the implementation of hand washing and self-report.[8,9]

Discipline is one of the cultural values of work in a military hospital environment that emphasises commitment and obedience to the rules and norms that apply in carrying out health services to patients and families. Discipline is behaviour and discipline by rules and regulations or behaviour obtained from training that is carried out continuously to improve the quality of nursing care.[10] Discipline is widely applied in various conditions to improve the attitude, mentality and motivation of nurses in improving the performance of health services in hospitals.[11,12]

This article was accepted: 11 April 2023
Corresponding Author: Kumoro Asto Lenggono
Email: kumoroasto72@gmail.com

This study aims to develop and empirically test the role of discipline as a mediating variable in the application of the *Theory Of Planned Behaviour* model of nurses' handwashing compliance in five moments six step hand washing behaviour.

MATERIALS AND METHODS

This research design used quantitative research with a survey approach that studies attitudes, beliefs, values, demographics, behaviour, opinions, habits, desires, ideas and other types of information. The reason for choosing the quantitative method is because it can cover various phenomena on the influence of intention and discipline variables with nurses' hand washing compliance behaviour which aims to test the application of the *Theory Of Planned Behaviour* on various variables studied. The TPB (Theory Of Planned Behaviour) model is used in this study because it can predict, explain and know the behaviour of nurses' hand washing. The population in this study was all nurses working in outpatient and inpatient installations totalling 321 people. Each service installation was taken proportionally where 16 inpatient service units totalled 108 nurses and 17 outpatient service units numbered 70 nurses using the Slovin's sample formula and a margin of error of 5%[13] so that the total sample was 178 nurses. The sampling technique used is proportional random sampling in each service unit outpatient and inpatient installations. Collecting data using surveys and observations on the quality audit of nurses' handwashing compliance by the hospital infection prevention and control committee through the Infection Prevention Control Link Nurse (IPCLN) officer in each room. The results were validated by the Infection Prevention Control Nurse (IPCN) committee.

Data analysis using structural equation modelling (SEM) with Smart Partial Least Square (SmartPLS) application. Mediation test analysis regression analysis of mediating variables using the product of coefficient method developed by Sobel. Therefore, this test is often referred to as the Sobel test. This test was carried out by testing the strength of the indirect influence of the intention variable (X1) on the implementation of hand washing (Y2) through discipline (X2), self-assessment (X3), and hand washing opportunities (Y1).[14]

Testing the significance of the indirect effect of the mediator variable on the dependent variable becomes (ab) with a standard error that will produce a statistical t value. To calculate the standard error ab, the following formula is used. While the t value of the ab coefficient is as follows: If the z test is above 1.96 (absolute z value standard), then there is a mediation effect. The mediation test was used to determine whether Nurse Discipline (X2) as an intervening variable played a role in mediating the Nurse's Intention (X1) variable on the Implementation of Nurse Handwashing (Y2).[14]

The involvement of mediating variables in a study has three criteria models:

1. Complete mediation, namely the independent variable, is not able to give a significant influence on the dependent variable directly without going through the mediating variable.
2. Partial mediation, namely the independent variable, can give a direct influence on the dependent variable without involving the mediating variable.
3. No mediation: There is no effect of mediating variables

The way to find out the value of the mediation variable can use the formula below.VAF = a x b/ a x b x c. The results of the calculations in the VAF formula are then adjusted to the criteria for the involvement of the research mediating variable in Table I.[15]

Ethical Approval

As a scientific activity that involves humans as subjects, this research had received ethical approval before data collection was carried out, namely from the Health Research Ethics Commission of *Poltekkes Kemenkes Malang,* Indonesia, 18/11/2022. Ethical approval was given based on the results of an evaluation conducted by the board of ethics examiners, which concluded that this study had implemented ethical principles of health research, including: upholding autonomy, not harming, maintaining justice and providing benefits to respondents. All participants also agreed to be involved as research subjects by completing informed consent, after previously being explained about the objectives and benefits of this study

RESULTS

All research hypotheses have a direct and positive significant effect, except for the hypothesised value of the Influence of Nurses' Intentions (X1) on the Implementation of Nurse Handwashing (Y2) with a SmartPLS Coefficient of 0.104. Given the p-value of 0.221 > 0.05, the coefficient is negative, meaning that the Nurse's Intention (X1) has no significance and negative effect on the Implementation of Nurse Handwashing (Y2). The higher the Nurse's Intention (X1), the lower the Nurse's Handwashing Implementation (Y2) (Figure 1).[16]

The indirect effect of Nurse Intentions (X1) on the Chances of Washing Nurse's Hands (Y1) through the mediation of Nurse Discipline (X2) with a direct effect coefficient value of 0.237 plus an indirect effect coefficient value of 0.186 = 0.423. Then the value of variance accounted for (VAF) is 0.186 : 0.423 = 0.440 or 44%. Considering the provision that the VAF value is between 20%≤ VAF <80%, it is concluded that nurse discipline (X2) is a partial mediating variable. The indirect effect of nurse intention (X1) on self assessment of handwashing (X3) through the mediation of nurse discipline (X2) with a direct effect coefficient value of 0.202 plus an indirect effect coefficient value of 0.286 = 0.488. Then the value of VAF is 0.202 : 0.488 = 0.414 or 41.4%. Considering the provision that the VAF value is between 20%≤VAF<80%, it is concluded that nurse discipline (X2) is a partially mediating variable. The indirect effect of Nurse Intention (X1) on the Implementation of nurse handwashing (Y2) through the mediation of nurse discipline (X2) with a direct effect coefficient value of 0.108 plus an indirect effect coefficient value of 0.444 = 0.552. Then the value of VAF is 0.444 : 0.552 = 0.8043 or 80.43%. Considering the provision

Table I: Variance accounted for (VAF) criteria

Criteria	Information
VAF < 20%	No mediation
20% ≤ VAF ≤ 80%	Partial mediation
VAF > 80%	Complete mediation

Source: SmartPLS Analysis Output Results, 2022[14]

Table II: Analysis smartPls indirect effect

	X1	X2	X3	Y1	Y2
X1			0.202	0.332	0.444
X2				0.098	0.181
X3					0.074
Y1					
Y2					

Source: SmartPLS Analysis Output Results, 2022[14]

that the VAF value is between 20%≤VAF<80%, it is concluded that nurse discipline (X2) is a complete mediation variable (Table II).[16]

The magnitude of the influence of nurses' intentions (X1), nurse discipline (X2), and self-assessment of handwashing (X3) on the opportunity of handwashing nurses (Y1) is 0.488 or 48.8%. The magnitude of the influence of nurses' intentions (X1), nurse discipline (X2), self-assessment of handwashing (X3), and nurse handwashing opportunities (Y1) on the implementation of nurse handwashing is 0.551 or 55.1% (Table III).[16]

DISCUSSION

The results of the SmartPLS analysis prove that the nurse's intention has no significant effect on the implementation of nurse handwashing with path coefficients of 0.104 and a p-value of 0.221 > 0.05. The coefficient value which is too small at 0.104 states that the nurse's intention to contribute to the implementation of nurse hand washing is only 10.4%. The rest comes from other variables. This means that the higher the nurse's intention tends to be able to increase the implementation of nurse hand washing, but the increase is not significant. The results of this study do not support research that states that intention has a significant effect on nurses' compliance with washing.[9,17–19] These results confirm the theory of planned behaviour which states that intention is a description of the motivational factors that a person has that underlies how hard a person tries to try and plan his efforts to display behaviour.[20,21] The empirical data of this study cannot prove that the high intention of nurses can increase the implementation of hand washing. This means that the higher the nurse's intention does not significantly increase the implementation of nurse hand washing. Age, education, attitude and gender can be factors that affect the nurse's intention to comply with hand washing.[22]

The nurse's intention to carry out handwashing is influenced by the variables of discipline mediation, self-assessment and the opportunity for nurses to wash their hands. This theory does not support the effect of intention on hand-washing compliance. Nurses' intentions do not always underlie the formation of nurse compliance in washing hands but are influenced by other variables in the formation of handwashing compliance. The existence of self-assessment and the opportunity to wash hands can reduce the risk of infection in the hospital.

The results of the SmartPLS analysis prove that the discipline of nurses has a significant positive effect on the implementation of hand washing. The path coefficients are 0.293 and the p-value is 0.000 > 0.05. The estimated value with a positive sign of 0.293 indicates that nurses with high hand-washing discipline will have high hand-washing practices as well. This study supports the discipline concept of Thomas Gordon[23] namely behaviour and discipline by the rules and regulations or behaviour obtained from training. Humans living in this world need norms and rules as guidelines and directions to climb the path of life, as well as nurses if a nurse wants high handwashing compliance then he must have discipline, especially high discipline. In this case, discipline is an attitude of respecting and obeying all. The results of this study are also in line with research studies that state that the impact of Covid 19 is that nurses are more disciplined and motivated in the performance and implementation of hand washing in hospitals.[24,25] He shows that nurses can be consistent in maintaining motivation and behavioural discipline in maintaining their performance in the health care workplace. The disciplinary approach to the nursing student learning process affects increasing learning comfort, self-confidence and nurse learning outcomes.[26] Obedience and discipline must be instilled and developed with willingness and sincerity so that skills will be truly possessed and the knowledge that is being demanded and learned can be understood and mastered perfectly. Every nurse must have high professional discipline in carrying out nursing care and midwifery care and apply professional ethics in practice. The professionalism of nursing staff can be improved by fostering and enforcing professional discipline and strengthening ethical values in professional life. In the perspective of nursing, the discipline of nursing is holistic, involving nurses, the environment and patients who are interrelated depending on and need each other to protect each other.[27] With high nurse discipline, it can increase compliance with hand washing five moments six steps. The implementation of hand washing five moments six steps for every health worker in a hospital is a standard procedure in infection prevention and control that must be carried out properly and correctly. The need to increase handwashing

compliance must be done through continuous education and training aimed at increasing handwashing awareness and compliance.[28] Monitoring and evaluation by carrying out a quality audit of hand washing carried out by the hospital's control and prevention committee is the key to successful supervision and development of health workers.[29]

Implementation of hand washing significantly. The effect of nurses' intentions on the implementation of nurses' hand washing through discipline is significant with a value of VAF of 0.8043 or 80.43%. Given the provisions of the VAF value between 20% and VAF <80%, it is concluded that nurse discipline is a complete mediation variable. Meanwhile, through self-assessment, it has a VAF value of 0.22.83% or 22.8%. So it can be concluded that the self-assessment of hand washing is a partial mediation variable (partial mediation). Meanwhile, the opportunity to wash hands has a VAF value of 0.15% or 15%. So it can be concluded that the opportunity to wash hands is a variable, not a mediating variable. Based on the results, the value of the discipline VFA coefficient is the perfect mediating variable for the formation of nurses' handwashing behaviour in the application of the *Theory Of Planned Behaviour*.

This finding confirms that the formation of handwashing compliance in nurses is not based on the nurse's intention but there is a role for the discipline variable as an intervening nurse's handwashing compliance. Discipline is seen as a condition that is created and formed through the process of a series of behaviours that show the values of obedience, obedience or order. These values have become part of behaviour in life. The behaviour is created through the fostered process through family, education and experience. Based on this opinion, it can be understood that discipline is something that is integrated within a person, even discipline is something that is part of a person's life that appears in his or her daily behaviour patterns.[30]

The results of this study state that nurses who have high discipline can improve compliance with hand washing five moments six steps well to increase compliance in carrying out their duties. In addition, discipline occurs and is formed as a result and impact of a fairly long coaching process carried out from within the family and service organisations in hospitals that are oriented towards providing excellent service to patients and the community.

The findings of this study also strengthen the concept of Gordon[31], discipline is a person's ability to obey the guidelines, Standard Operating Procedures and rules that have been set by the hospital. With discipline, it can form behaviour and discipline by the rules and regulations, or behaviour obtained from training that is carried out continuously. Because to achieve compliance with nurses' hand washing five moments six steps not only requires strong intentions but also requires discipline as an intervening variable mediating the Theory Planned Behaviour application for the formation of nurse handwashing compliance behaviour. Nursing discipline is the focus and centre for the health of everyone and is a protector for people who need health and nursing services.[32]

CONCLUSION

Discipline is a perfect mediating variable in the application of the theory of planned behaviour in the compliance of nurses' hand washing five moments six steps.

ACKNOWLEGMENT

I would like to express a very high appreciation to Dr. Moh. Hafid Akbar, Sp.JP(K) as head of the military hospital Dr. Soperaoen Malang. I would also like to express special thanks to the promoter, team and colleagues from the hospital infection prevention and control committee, and I am very grateful for the assistance provided by the academic staff of the Doctoral Program at the Post Graduate School of Environmental Sciences, Brawijaya University Indonesia.

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Perception, views, and barriers of primary care doctors regarding screening of depression among elderly patients attending public healthcare clinics in Kuching district: a qualitative study

Benjamin Teh Wee Chuan, MBBS[1,2], Aznida Firzah Abdul Aziz, PhD[1], Mohd Fairuz Ali, MMed[1]

[1]Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [2]Klinik Kesihatan Kota Samarahan, Ministry of Health, Malaysia

ABSTRACT

Introduction: Depression in the elderly constitutes 7.3% of the total Malaysian national prevalence of depression. However, depression is commonly underdiagnosed by primary care physicians, which may impact coexisting comorbid conditions and general well-being. As depression in the elderly increases with age, its prevalence is expected to become even more significant due to the increased life expectancy and isolation during the pandemic. This study aims to determine the perceptions, views and barriers encountered among primary care physicians on screening for depression among the elderly.

Materials and Methods: This qualitative study involved five public healthcare clinics in the Kuching district with in-depth interviews (IDI) conducted on 14 primary care doctors (PCDs). Semi-structured interviews and in-depth discussions were conducted via videoconferencing. One representative was selected from each clinic at initiation, followed by snowball method for subsequent subject selection until saturation of themes. Interviews were transcribed verbatim, and analysis based on framework analysis principles via NVivo software. Themes were analysed deductively according to study objectives and evidence from literature.

Results: Three main themes emerged from the IDI: (1) The perception of depression in elderly patients, (2) The perceived barriers to screening, and (3) The screening processes. Majority of the PCDs perceived depression as part of ageing process. Time constraints, lack of privacy in consultation rooms, dominant caregivers and failure to recognise recurrent somatic symptoms as part of depression influenced PCDs decision to screen. Screening was technically challenging for PCDs to use the DASS-21, which was not socio-culturally validated for local native population. Only 21.4% of respondents (3/14) reported screening at least three out 10 elderly patients seen over 1-month period. During the covid pandemic, due to the same human resource support and practices, most participants thought their screening for depression in elderlies had not changed.

Conclusion: Awareness of depression among PCDs needs to be re-enforced via continuous medical education programs to use appropriate screening tools, address infrastructure related barriers to optimise screening practices. The use of appropriate locally validated and socio-culturally adapted tool is vital to correctly interpret the screening test for patients.

KEYWORDS:
Perception, primary care doctors, screening, depression, elderly patients, healthcare

INTRODUCTION

Ageing is an inevitable life process, reflecting the body's physical and psychological changes over time. Depression in the elderly is common and highly prevalent. According to National Health and Morbidity Survey (NHMS) in 2019, the prevalence of depression among Malaysians aged 18 years and above was 2.3%, and among those aged 60 years and above was 7.3%.[1]

Like the other age groups, the elderly population is not exempted from getting depression, and study has shown that the prevalence of depressive illness increases with age and is expected to become an even more significant concern due to the decline in mortality and fertility rates and the improvement in quality of life.[2]

In Malaysia, as in most healthcare systems, primary care doctors (PCD) are the first point of access to healthcare, providing treatment for most non-communicable diseases (NCD) and referral to specialists such as psychiatrists. Although PCDs treat more elderly patients than younger patients, depression is less likely to be detected among the elderly than younger patients in the primary care setting.[3]

Many of the PCDs may lack the necessary skills or confidence in detecting depression in the elderly. A study done in Saudi Arabia showed that 30% of the PCDs had poor knowledge of geriatric depression[4] and similarly, in Japan, Othsuki and colleagues found that doctors seldom diagnosed depression in their patients; in fact, majority of the individuals diagnosed with a mood illness were not given antidepressants.[5]

This article was accepted: 15 April 2023
Corresponding Author: Dr Aznida Firzah Abdul Aziz
Email: draznida@ppukm.ukm.edu.my

In December 2019, the world geared up to fight against the COVID-19 virus health emergency as the pandemic rapidly spread globally, and even the wealthiest countries' health systems were under pressure to respond to the enormous needs of the vulnerable elderly patients. The Malaysian government implemented nationwide Movement Control Order (MCO) on 18 March 2020 to curb the spread of disease. The elderly were constrained from visiting family members, social participation was not allowed, and access to healthcare for non-covid symptoms or NCD monitoring was compromised to a certain extent.

During MCO, not just physical activity was affected, but also mental health. Several earlier studies done during mandatory quarantine and social isolation measures have shown a higher risk of depression, emotional disturbances, stress, low mood, irritability and insomnia.[6,7]

To formulate strategies to improve the recognition of depression among the elderly, we need a better understanding of the PCD's perceptions and views in screening for depression among their elderly patients.

Until now, studies which evaluate the perception and views of PCDs regarding the screening of depression among the elderly in Malaysia are scarce. Thus, this study aimed to explore PCDs' perceptions, screening strategies and barriers in screening for depression among elderlies to enable practical suggestions to improve clinical detection and management of elderly with depression attending primary healthcare clinics.

MATERIALS AND METHODS

Study Design

A qualitative study was conducted, using in-depth interviews (IDI) to obtain the perception and views of PCDs regarding screening of depression among elderly patients attending public healthcare clinics in the Kuching district, Sarawak, Malaysia

Study Setting

This study was conducted at five primary public healthcare clinics located in Kuching district, Sarawak, Malaysia: Klinik Kesihatan Petrajaya, Klinik Kesihatan Batu Kawa, Klinik Kesihatan Jalan Masjid, Klinik Kesihatan Tanah Puteh and Klinik Kesihatan Kota Sentosa.

Participants

Study participants were medical officers' (grade UD44 and above) who have worked at least 6 months in a public healthcare clinic in Kuching District. Family medicine specialists, house officers or allied health personnel (i.e., pharmacist/nurses/medical assistants) were excluded from this study. One representative was selected from each clinic at initiation, followed by snowball method for subsequent subject selection until saturation of themes.

Approvals were obtained from the Universiti Kebangsaan Malaysia Ethics committee (Research ID: JEP-2021-598), the Malaysian Ministry of Health Medical Research, Ethics Committee (MREC) National Medical Research Registry (NMRR ID-21-01945-7WC) . Permission to conduct the study was also obtained from the state health authority, i.e., Jabatan Kesihatan Negeri Sarawak (JKNS) and Pejabat Kesihatan Bahagian (PKB) Kuching, Sarawak.

Data Collection

Data collection took place between July and August 2022. Interviews were conducted using semi structured questions which were vetted by the research team. A pilot test involving two medical officers and two researchers was conducted to ensure that the questions were well understood and allowed participants to further elaborate on the questions asked. Minor adjustments were made to rephrase a few questions before the study commenced. The pilot testing sessions were not included in the final analysis. All videotaped interviews were transcribed verbatim. All interviews lasted between 30 minutes to 60 minutes and were carried out via zoom video calls with two researchers (Researchers involved are listed in Appendix 1). Transcriptions were checked with video recordings for accuracy prior to analysis.

Saturation of themes was decided when no new themes appeared in the interviews, and this was established by the 14th participant.

Two researchers reviewed the transcripts separately and coded the emerging themes using N-VIVO software. Data collection and analysis were conducted simultaneously until data saturation was achieved. All the data that had been coded were grouped based on potential themes, and main themes and subthemes were identified. The analysed codes and themes were then discussed with a third member of the research team to achieve consensus on the interpretation of the data.

All the participants were informed that the interviews would be recorded, and all the participants gave verbal consent as well as signed the informed consent which was sent via email to the researcher.

RESULTS

Demography of Participants

This study presents the results and analysis of interviews conducted with 14 PCDs in Kuching. The mean age of the participants is 35.2 (SD 4.54) years, who have been practicing as primary care providers for mean of 9.86 (SD 5.08) years. The sociodemographic profile and training background details are listed in Table I.

The Perception of Depression in elderly patients

PCD's views on depression among their elderly patients were a crucial factor in determining how they managed patients in this age group. Most of the PCDs regarded depression as part of ageing. The doctors described that as a person ages, the lack of social support, physical limitation, deteriorating vision, hearing difficulties and "empty nest syndrome", where they feel lonely after their children leave home to pursue their careers and livelihood prevail:

> *"The future generation will want to have a development in their career so those who are left behind are the parents, the parents will be ageing and left in the village and somehow get abandoned and of course…(P2)*

Table I: Participants' sociodemographic (N = 14)

Participants	Gender	Age	Duration of practice (years)	Experience in attending geriatric attachment/training/course
P1	Female	34	9	No
P2	Male	42	19	No
P3	Female	38	12	No
P4	Male	32	6	No
P5	Female	35	8	Yes
P6	Female	37	12	Yes
P7	Female	34	7	No
P8	Female	31	6	No
P9	Female	30	3	No
P10	Female	36	11	Yes
P11	Male	36	11	Yes
P12	Male	46	21	No
P13	Female	31	8	No
P14	Female	31	5	No

Table II: Themes

Themes	Transcripts
The perceptions of depression in elderly patients	
Awareness	Nowadays, the MOs are more open on depression, so I guess they do kind have a better idea on depression in elderly, so the screening is better. -P3 I think the awareness regarding mental health has increased after COVID-19. More patients appear with mental issues, after COVID-19. Even in young patients…-P6
Aetiology of depression in elderlies	The future generation will want to have a development in their career so those who are left behind are the parents, the parents will be ageing and left in the village and somehow get abandoned and of course, depression will be there for them. –P2 Most patients will say that it's part of the ageing process, it's just normal for them. -P9 I think there is a strong relationship between ageing and depression… ageing adults that must cope with certain difficulties, so this will play an important role that can trigger the depression in the elderly…We can't deny the relationship between ageing and depression; very strong correlation. -P12
The need to screen the elderlies	For me, yes, it is very important for the healthcare doctors to do the screening in the elderly for depression... -P3 Yes. Ideally, we should be screening everyone. That is the ideal situation where the doctor-to-patient population is good, clinic is not so busy, and you can spend more time with each patient. –P11
The perceived barriers to screening	
Patient-related barriers	"… think is a challenge is family members…some family members don't really agree that their parents are having depression symptoms. They kind of deny it but the parents keep telling us that "I cannot sleep la Dr", the family members keep saying, "dia minum coffee Dr that's why tak boleh tidur"…, it's quite hard when the anak is denying the parents punya complain. So, the parents just tend to shut down and don't tell you anything anymore…" -P3 "… the elderly doesn't understand the DASS-21 score (items), and we must explain one by one with that also, they don't come up with a good answer." -P7 "…patients are accompanied by another relative and not the main caretaker, it is difficult to get history from the patient." -P6 "they just want to vent…For example, they are having trouble sleeping sometimes, it is very similar to symptoms of depression also. So, that can be confusing for me, if it's not clear-cut depression unless it's very severe." -P13
Doctors, infrastructure, and system-related barriers	"…the lack of knowledge. Initially, when I first started, I didn't have much knowledge to screen these elderly patients." -P4 "As you know in Sarawak, there are lots of local people, Bidayuh, Iban, so when you try and use the DASS-21 screening…I would have to translate it to their language because some can't understand English or BM, they only know the Iban, Bidayuh and local language. So, these are the problems that can arise." -P2

cont..... pg 304

cont from..... pg 303

Table II: Themes.

	"It is a challenge for us in a busy clinic, it is very hard to tackle the problem of depression because they come in for their primary problems, NCD follow-ups and other acute problems but the area of depression is something we lack in time to go into." -P10 "Most of the MO s are sharing rooms, at most there are 2 MOs per room, maybe 3 with a houseman, with that current setting there is not much privacy. Very difficult to probe for depression."-P11
The Screening Processes	
Screening tools	"… we have this yearly screening for Saringan Kesihatan Warga Emas and will include DASS-21" -P7 "I try to use the Geriatric Depression Scale (GDS), I find that easier than the DASS-21." -P9 "I will still use either the GDS or the Patient Health Questionnaire. But I prefer to use the Patient Health Questionnaire..." -P4
Strategies for screening and managing depression in elderlies	"If the symptoms are suggestive, then I will arrange another TCA where we have more free time, especially on Fridays… we will have the time to get more history..." -P8 "The more you have a good relationship with the elderly, the better your communication skills are with the elderly." -P3
Impact of COVID-19 pandemic on screening for depression among elderly	"I think almost the same – doesn't really change pre-COVID and the current situation." -P7 "Changed somehow because we have started to do visual consultations so we would have appointments for those stable patients with chronic diseases to follow up through visual consultation… screening for depression in the elderly either through Zoom or through the phone" -P1

Most of the PCDs are aware of the importance of screening for depression among their elderly patients, and mental health awareness has increased among the healthcare providers and the community, especially after the COVID-19 pandemic and lockdown. They felt that the elderly is prone to depression and should be screened opportunistically and regularly, and they are confident in detecting and diagnosing depression. However, not many were able to do screening due to limited time and daily busy clinic services:

> *"It is a challenge for us in a busy clinic… because they come in for their primary problems, … other acute problems but the area of depression is something we lack in time to go into."* (P11)

The Perceived Barriers to Screening

In doctor-related barriers, most of the PCDs perceived that screening for depression in the elderly is very time-consuming where history taking has to be comprehensive, and they do not have the time to perform it during their daily practice:

> *"Routinely no…In one hour, we probably have to see more than 5 patients, no time to really screen for depression…* (P13)

A few of the PCDs questioned the validity of using "self-translated" version of the screening tools such as Depression Anxiety Stress Scale -21 (DASS-21) into the local Sarawak native languages such as Iban and Bidayuh. This raised some concern as some of these groups expressed their emotions and interpreted words and terms differently, in their native language:

> *"As you know in Sarawak, there are lots of local people, Bidayuh, Iban, so when you try and use the DASS-21 screening… is it valid for us to use our own interpretation and translation in using those tools..."* (P2)

One PCD mentioned that he was not confident in performing screening and diagnosing of depression because of a lack of knowledge and training regarding this:

> *"…the lack of knowledge…I didn't have much knowledge to screen these elderly patients..."* (P4)

Many of the PCDs expressed that one of the barriers in screening during their consultation was the lack of privacy in the consultation room as they had to share one room with two to three other PCDs, and that made it very crowded and compromised confidentiality:

> *"…issue with space in my clinic because in my room I have three (3*) MOs*…"* (P9) *(*medical officers)*

Family members' attitudes could be a barrier to elderly patients to express their feelings and symptoms. P10 mentioned that the accompanying relative would dominate the consultation by just telling the history and not allow the elderly patient to participate in the session, leaving the parent/patient to remain silent throughout the consultation.

However, P2 mentioned that at times if the elderly patient comes alone, it is also challenging to attain history due to the language barrier and hence affects the accuracy of making the diagnosis:

> *"If the patients coming alone…there is communication barrier also, it is not that confident to me to further assess whether there is a symptom of depression."* (P2)

P1 reported that patients themselves would be afraid of social stigmatisation if the diagnosis of depression is being made to them, and it poses a significant challenge if the patient is not ready to come forward while in the denial phase:

"…Some may feel that they are being stigmatised or maybe they are not ready to be known that they are depressed." (P1)

Many PCDs described difficulties in screening and diagnosing depression in elderly as the elderly patients tend to present with many vasomotor symptoms for each visit, and hence challenging to differentiate between physical illness and depression as the real diagnosis.

The Screening Processes

Good rapport with the patient is considered crucial in the screening and diagnostic process. Most PCDs reported that they had developed their own routine and questioning approach based on intuition and observation and will re-arrange another appointment to explore further:

"…the one thing I think is the most problematic one is rapport. You don't have a rapport with the elderly, they don't want to tell you anything." (P3)

Depression Anxiety Stress Scale -21 (DASS-21) and Geriatric Depression Scale (GDS) were the most widely used screening tools by most participants in their daily practices. The screening program reported by P2 refers to the use of the DASS-21 questionnaire in the Ministry of Health (MOH) Borang Saringan Status Kesihatan Warga Emas (BSSK) booklet, which is an annual screening requirement for all the elderly patients attending public primary health centres and a measure of the facility's key performance index (KPI)

"… Through this regular yearly Warga emas BSSK routine screening…, so we put the questionnaire, the DASS-21 alongside the BSSK..." (P2)

Patient Health Questionnaire–9 (PHQ-9) was also part of the PEKA B40 (Skim peduli kesihatan untuk kumpulan B40) application form where elderly patent would be opportunistically screened for depressive symptoms upon application:

"… when they come to do the Peka B40, the initial part, the first screening ya they have the PHQ-9 there." (P4)

Only one participant (P5) reported using Beck Depression Inventory (BDI) in screening. If there is any language barrier in translating to another language, they will require assistance from colleagues from the same ethnicity to directly translate the screening questions:

"For Chinese, we ask our colleagues to converse in Chinese. We usually bring them to another room or a corner wherever they can to have time to talk to screen them." (P12)

When prompted for the number of screenings per month out of 10 elderly patients seen, only three participants had screened three patients and more for depression:

"For the last one month, I don't think I screened any depression in patients aged more than 60 but less than that I have." (P8)

"About 3-4 patients. Quite commonly I would ask their mood. 3 out of 10." (P10)

Most of the participants felt that their practice of screening for depression in elderlies had not changed before and during the COVID-19 era, mainly due to the same human resource support and practices:

"I think my practice of screening has not changed because workload is back to usual, the number of patients is a lot compared to the amount of manpower." (P13)

DISCUSSION

This qualitative study presents an in-depth exploration and views of PCDs in screening for depression in elderly patients. The World Health Organisation (WHO) defines NCDs as non-transmissible medical disorders, often also known as chronic diseases, which are long-term illnesses caused by a mix of genetic, physiological, environmental and behavioural factors.[8] While this classification has incorporated a variety of medical diseases, the emphasis of NCD has largely always been four conditions: cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), cancer and chronic respiratory diseases. In 2018, the United Nations member states expanded the NCD umbrella to include mental health disorders.[9] Meta-analyses have shown associations between diabetes and mental illnesses such as depression and bipolar disorder, as well as between diabetes and cognitive impairment.[10] Improved screening and treatment for depression among our elderly patients will not only help to optimise NCD care such as diabetes and hypertension but will also improve their quality of life.

The strong association between mental health illnesses and other NCDs call for multi-disciplinary care between primary, secondary care and allied health services. Collaborative care models have emerged as an effective evidence-based method for integrating mental health services into primary care settings.[11] In 2019, Klinik Kesihatan Kota Samarahan, Sarawak, launched a geriatric clinic in primary care named "Geriatrik Komuniti – GeKo" to specifically handle geriatric patients 60 years and above with frailty and complex bio-psycho-social issues.[12] Training was provided to PCDs and allied healthcare personnel to detect and manage geriatrics issues. This initiative empowers healthcare providers, elderlies and families to improve the elderly's health. Besides that, Klinik Kesihatan Petrajaya, Kuching, has a collaborative care unit with community psychiatry named MENTARI, where a visiting psychiatrist from the tertiary hospital provides on-site shared care initiative to the primary care team. When mental health treatment and NCD care are integrated and implemented in the primary care setting, it is effective for patients, strengthens healthcare delivery systems, and reduces costs in the long run.[9]

The majority of respondents mainly mentioned two significant factors for doctor-related barriers: time constraints in exploring depressive symptoms and infrastructure barriers such as lack of consultation rooms causing the lack of privacy during consultation as three PCDs have to share one small consultation room together and see patients simultaneously. Lack of time is the most recurring theme of all the respondents, with a total of 41 references made. PCDs perceived screening of depression as time-consuming and required additional time for history taking. Most screening

questionnaires take time to fill up, and in a busy primary healthcare setting where the PCD only has limited time to attend to each patient, this could be a significant obstacle in screening for depression in older people. Since 2023, DASS-21 has been replaced by Whooley, which is shorter, has only two questions, and has been validated for use in primary care as a screening tool. Besides that, Orleans and colleagues concluded that from a study exploring the perception on barriers to treating mental illness, physicians reported patient resistance and time constraints as the most significant hurdles to mental health treatment in primary care.[13]

There are many instruments to screen for depression in the elderly, including the most commonly used: the GDS, which is shown to have a sensitivity of 92% and specificity of 89%.[19] GDS has been validated in many languages and suitable for use in community, acute and also long-term care settings. The tool that is used for screening must consider the logistic challenges apart from its ability to screen, diagnose and aid in monitoring the progress of patients diagnosed with depression. The 14-item Malay version of GDS (M-GDS-14) reported 100% sensitivity and 92% specificity in detecting major depression.[15] However, the participants questioned the validity of the results of the screening program among ethnic groups in East Malaysia, and the accuracy of its results as doubtful.

In the primary care setting, elderly patients usually come with many somatic symptoms and do not directly complain of mood symptoms which may mask the underlying disease.[3] In all studies, depressive symptoms in the elderly were described as unspecified and often concealed by somatic symptoms. Patients seen in primary care often present with ambiguous symptoms, which could potentially be many other diseases, including depression.[16] Diagnosing depression by PCD involves several conversations with patients and families that are often complex and demand high experience-based skills.

To detect a milder form of depression, PCD is likely to rely on clinical judgement compared to formal objective assessment, and they highlighted the importance of establishing a good rapport and knowing the patient holistically. Depression differs from other medical illnesses for which there are objective diagnostic tests and measurable treatment responses.[17]

Professional knowledge and skills were deemed essential for the screening, diagnosis and treatment process. The majority of PCDs in the study felt that there was a lack of training and knowledge on how to screen, diagnose and manage depression in elderly patients. No CME, teaching, or guidance was provided in this matter. To improve the screening and treatment for depression in the elderly, more systematic training and awareness need to be done by primary healthcare providers. If equipped with these competencies, PCD can have a greater awareness, skill, and confidence in detecting and managing elderly with depression.

This study has identified several gaps in knowledge and practice of PCDs on depression screening in older people. Some of the participants interviewed were unsure; generally, the type of tool to screen for depression in the elderly was not Mini-Mental State Examination (MMSE)/Montreal Cognitive Assessment (MOCA). Inappropriate tools were being used for screening depression. CME dedicated to using simplified, locally validated and more reliable tools such as GDS should be organised for PCDs. Self-reported checklists such as BDI and GDS has high specificity and sensitivity.[18,19] yet only one participant used BDI and four used GDS.

The quality of the translation was questioned by most participants, mainly when translating it into the native language of Sarawak, where there are 26 different ethnicities, and 40% of the population are made up of indigenous communities called “Dayak”. Furthermore, some ethnicities have different words to describe their feelings and emotions, which might have led to misinterpretation and the validity of such data collection. This suggests that due diligence is required for the translation process to ensure accurate results obtained from the screening. Bearing in mind that some ethnicities do not have a description for depression or feeling sad. Future research should focus on adapting current screening tools into local native language with accurate representation of local contexts. It could come in handy, especially in primary healthcare clinics in Sarawak's rural areas, by having a tool which is adapted to local socio-cultural norms. Henceforth, KPI for mental health screening targets in Sarawak states should be carefully interpreted based on the issues of the existing tool’s validity and language-related barriers. There is a need to perhaps reconsider the DASS-21 as a screening tool for elderly in the Malaysian community as it might not be suitable across the various multi-ethnic groups which exist in Peninsular and East Malaysia and for the reasons stated earlier. After data collection concluded, in January 2023, the Health Department of Sarawak has implemented Whooley-2-question screening as a standardised screening tool in primary care. The screening of depression using Whooley’s questionnaire in primary care documented a sensitivity of 99% and specificity of 70% and has been validated locally in Malay.[20] However, to date, Whooley’s questionnaire has not been translated into Dayak or any other native Borneo language.

Most respondents felt that there was no change during and after covid pandemic because the main issues were time constraints and lack of supportive resources to actively screen for depression challenged by the heavy work burden and deployment of clinic staff to manage the infection and hence the screening of depression was compromised.

This study, to the best of our knowledge, is the first qualitative study done to explore the perception and views of PCDs in Malaysia regarding screening of depression in elderly patients receiving treatment at public primary healthcare clinics. This study further reinforces the outcome of prior research undertaken in other parts of the world. The research was carried out in Sarawak with a great diversity of ethnicities, demonstrating the need for a screening tool and diagnosis algorithm that factors into local culture and community understanding. The main limitation of this study is that only participants from the capital of Sarawak, Kuching, were enrolled; hence it may not be truly reflective of the general population. Although participants were only

recruited from one district, it provides insight into strategies and policy implementation for future studies.

CONCLUSION

This paper presents the findings of exploring the current views and perceptions of primary care doctors (PCDs) regarding screening of depression in elderly patients. PCDs believe that elderly patients should be screened for depression, however, many reported that time and limited manpower with inconducive consultation room as the main barrier.

Many PCDs doubt the validity of the tool's translation into local dialect in primary care settings with diverse ethnic and cultural characteristics. Recommendation for a shorter screening tool that is socioculturally acceptable, able to correctly screen and detect depression among the elderly local population is vital.

Raising awareness among caregivers of elderly patients in particular regarding depression not being part of normal ageing and somatic symptoms of depression may predominate and warrant further investigation. There is a need for caregivers to realise that these symptoms must be discussed with PCDs to prompt timely intervention in the busy primary care clinic. Likewise, there is also a need for PCDs to be exposed to geriatric depression training programs and continuous medical education sessions to use the appropriate screening tools. The program must prioritise on increasing PCD knowledge and management skills in screening, diagnosing, and managing depression in the elderly.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Ministry of Health for his permission to publish. We thank Dr Sally Suriani Ahip, Family Medicine Specialist at Klinik Kesihatan Kota Samarahan for her input during proposal development.

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ORIGINAL ARTICLE

Effectiveness of health education module on work safety culture in improving knowledge, attitudes and practices: a cluster randomized controlled trial among public sector administrative workers in Nigeria

Josiah Oluwaseun Odu, PhD[1], Titi Rahmawati Hamedon, MD[1], Aidalina Mahmud, PhD[2], Mohd Rafee Baharudin, PhD[3]

[1]Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, UPM Serdang Darul Ehsan, Malaysia, [2]Occupational Safety and Health Management Office, Universiti Putra Malaysia, Serdang Darul Ehsan, Malaysia

ABSTRACT

Introduction: Studies have shown that a workplace safety culture (WSC) is lacking among the general workforce in Nigeria. Poor WSC can adversely impact workers' health and high remedial costs for employers. To improve WSC, workers need to improve related knowledge, attitude, and practices (KAP) towards WSC through effective health interventional programs at the workplace. The main objective of this study is to develop, implement and evaluate the effectiveness of the Work Safety Culture Health Education Module (WSCHEM). The specific goals are to improve KAP related to office ergonomics towards WSC among public sector administrative workers in Abeokuta, Nigeria

Materials and Methods: The study was a two-armed, single-blinded cluster randomised controlled trial (CRCT) involving 247 public sector administrative workers from clusters of 20 ministries in Abeokuta, Southwestern Nigeria. The intervention group was given WSCHEM, whereas the waitlist group received a seminar on team building and leadership skills and received the WSCHEM after the intervention program ended. The evaluation was done three times using the first formal validated, self-administered Work Safety Culture Questionnaire (WSCQ) among the administrative workers: first at baseline, second at 1 month, and third at 3 months post-intervention.

Result: The results showed no statistically significant differences between groups regarding the respondents' characteristics (socio-demographic and occupational/office-related ergonomic factors) and the outcome variables KAP towards WSC at baseline. For practices towards WSC, both intervention (β 6.8, 95%CI 4.85, 8.72) and time (β 6.2, 95%CI 4.49, 7.94) significantly improved the respondents' practices towards WSC in the per-protocol analysis. In the secondary outcomes, both knowledge of WSC, intervention (β 3.5, 95%CI 2.8, 4.2) and time (β 3.4, 95%CI 2.7, 5.9); and attitudes towards WSC, intervention (β1.7, 95%CI 1.25, 2.23) and time (β 2.3, 95%CI 1.92, 2.76) significantly improved the respondents' level of knowledge and attitudes respectively towards WSC.

Conclusion: The intervention, WSCHEM, was effective in improving the administrative workers' KAP towards WSC, as demonstrated by the significance between and within-group differences.

KEYWORDS:
Administrative workers, office workers, work safety culture, health education, knowledge, attitude, and practices towards work safety culture

INTRODUCTION

Workplace safety culture (WSC) is crucial in providing a safe working environment. Workers need to be regularly reminded of its importance, and therefore an effective WSC health education program must be identified for this purpose. Based on the global worker health plan of action, the World Health Organisation (WHO) strongly encourages the education of workers, employers, primary care practitioners and professionals for occupational services, and workers' health should be integrated into the basic training for health care.[1]

Training is essential in ensuring and enhancing worker safety, including office workers. However, an effective health interventional program to assess the effectiveness of the Workplace Safety Culture Health Education Module (WSCHEM) on knowledge attitudes and its practices (KAP) among administrative (office workers) is needed to minimise the escalating medical cost of managing occupational health problems (diseases and accidents) related to the poor WSC among them.[2]

"Workplace safety culture can be construed to be manifested in shared values and meanings, and in a particular organizational structure and processes, safety policies, strategies, goals, practices, and leadership styles related to the safety management system."[3] "Workplace safety culture refers to the enduring value, priority, and commitment placed on safety by every individual and every group at every level of the organization."[4] Workplace safety culture is a part of the corporate culture of every organization. "It has been described by the phrase, how we do things around here."[5]

This article was accepted: 20 April 2023
Corresponding Author: Josiah Oluwaseun Odu
Email: seun_odu2001@yahoo.com or gs54933@student.upm.edu.my

Health and safety commission[6] defines "Workplace safety culture as the product of individual and group values, attitudes, competencies, and patterns of behavior that determine the commitment to, and the style and proficiency of, an organization's health and safety management." Workplace-related disasters such as accidents, injury, and disease result from a breakdown in an organization's policies and procedures to deal with safety. The collapse flows from inadequate attention paid to WSC to make the workplace safe for everyone. "For example, a result of the accident investigation in Chernobyl revealed many irregularities in the organizational WSC."[7] Workplace safety culture is precisely planned to minimize the rate of susceptibility to diseases/accidents/injuries or occupational health problems at the workplace

As a result of the high prevalence of occupational health problems and high economic burdens caused by poor WSC in every organisation, primary prevention strategies to address the issues are paramount. Therefore, intervention programs on knowledge, attitude, and practices KAP towards WSC are needed by all the organisations to create a safe working environment and also help to reduce the exposure of workers and the general public to occupational health problems in the workplace.[8-9]

Although WSC is more important in high-risk working environments such as the construction industries,[10] medical and health care centers,[11-12] and aviation industries.[13] Its role among office workers is also essential because of the nature of the office work. Office workers spend extended periods remaining sedentary while working, often sitting for hours in front of computers and under unfavourable ergonomic conditions.[14]

The report from ILO 2019 reported that 36 (%) of workers work excessively long hours, meaning more than 48 hours per week; the report highlighted that office workers are particularly more at risk.[15]

In Malaysia, the Department of Occupational Safety and Health (DOSH) (2016) reported occupational-related diseases among workers in the country. The report showed that the total number of occupational diseases reported increased from 13.8% in 2012 to 19.9% in 2013 and 20.4% in 2014, and finally rose to 45.9% in 2015 in the country.[16]

In Nigeria, the Nigeria Social Insurance Trust Fund (NSITF) also reported that in the first 9 months of 2016, the fatality recorded by NSITF was 38.2% compared to the entire years of 2014 (12.6%) and 2015 (34.5%). The cases were low prior to the year 2016.[17] However, another study showed that the lack of a culture of safety and inconsistency in Nigeria's health and safety laws are the major factors that contributed to increasing cases of occupational diseases and fatalities in the country.[18]

As for office workers, many physical injuries and disorders exist among them. For example, posture problems from sitting or standing too long in a static position, vision difficulties from gazing at a computer screen for prolonged periods, and musculoskeletal disorders.[19-21] To reduce these problems and instill a more positive WSC so that the work conditions and environment are safe and healthy, the workers must have high knowledge, a positive attitude and good practices towards WSC. Therefore, a workplace health education intervention would be a reasonable effort in increasing KAP towards WSC among office workers in Nigeria.

This study's main objective is to develop, implement and evaluate the effectiveness of the WSCHEM. The specific goals are to improve KAP related to office ergonomics towards WSC among public sector administrative workers in Abeokuta, Nigeria.

MATERIALS AND METHODS

The study was a two-armed, single-blinded cluster randomised controlled trial (CRCT) involving 247 public sector administrative workers (office workers) recruited from all the 20 ministries (clusters) in Abeokuta, Nigeria. The clusters in this study refer to the government ministries in the state. The respondents and the clusters were blinded, while the researcher was not. Allocation concealment was achieved by enclosing group allocation in the random sequential numbered with sealed envelopes. Blinding was done by ensuring that the respondents were unaware of the randomisation assignment during the enrolment and follow-up period. Therefore, the programs for both the intervention and waitlist groups took place concurrently during the study periods in different sites (halls).

For the intervention, the researcher delivered the WSCHEM program. As for the waitlist group, one of the senior administrative workers (director) and one of the research assistants from the Ministry of Finance delivered the seminar on team building and leadership skills. The waitlist group also received the WSCHEM after the intervention program ended and was delivered by the researcher. All the respondents were followed for 1 month and 3 months after enrollment in the study.

Participants

The study population is all administrative workers working in 20 government ministries in Abeokuta, Southwestern Nigeria. All the office workers on any leave during the data collection and intervention program period were not included.

Procedure

The CRCT was conducted in which the total number of clusters in this study was 20. A statistician who worked at the Medical Records Department of State Hospital, Abeokuta, Ogun State, Nigeria, randomised the clusters into the intervention and waitlist groups.

The ratio of the intervention group to the waitlist group applied in this study was one-to-one. The 20 clusters were listed in alphabetical order and numbered from 1 to 20, and each of these 20 clusters was given a randomly selected opaque, sealed envelope. Inside each envelope was the note that assigned the cluster to either the intervention or waitlist groups. At the end of the randomisation process, 10 clusters

were randomly allocated to the intervention group, and another 10 were allocated to the waitlist group. Figure 1 displays the flow of participants throughout the study.

The list of office workers was obtained from each cluster from the respective administration office. First, the names in the list were numbered and acted as the sampling frame; respondents were randomly selected from the list of administrative workers for each ministry using the random number generator. A total of 247 informed consent were obtained from a total of 386 eligible office workers. Baseline data collection was then carried out among the 247 respondents.

As shown in Figure 1, 20 government ministries with 460 administrative workers were assessed for eligibility before study. The administrative workers who had neither fulfilled the eligibility criteria (74) nor consented (139) to participation were excluded from the trial. There were 122 respondents in the intervention group and 125 respondents in the waitlist group who had agreed to be recruited into the study. During the follow-up period, seven respondents did not turn up from the intervention group, and eight respondents from the waitlist group were lost to follow-up for various reasons. Thus, the response rate was 94.3% for the intervention group and 93.6% for the waitlist group.

Intervention

In the first step of developing the intervention module, a situational analysis was done in terms of the relevance of WSC among the administrative workers (office workers) and the necessity for intervention. The literature review and

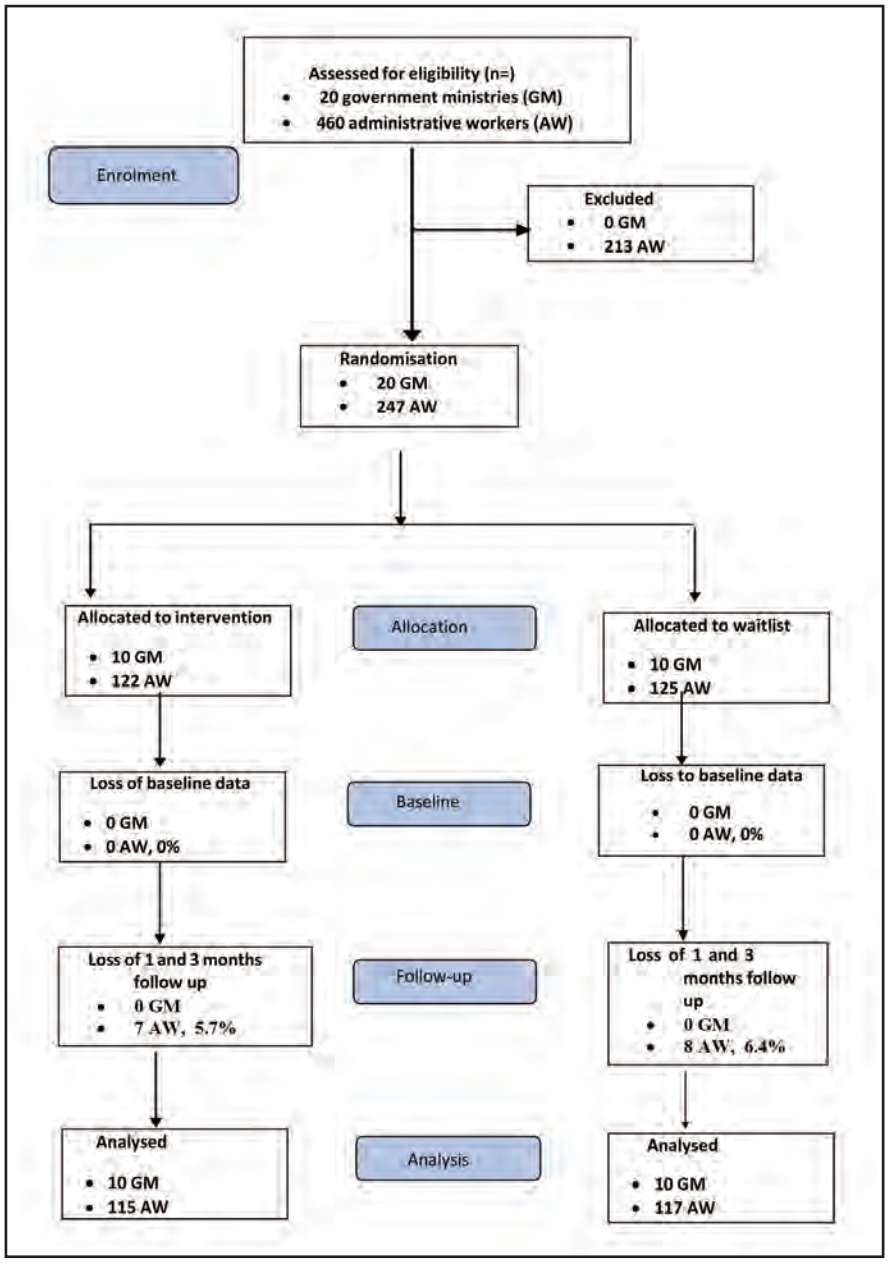

Fig. 1: Cluster randomised controlled trial flow chart.

reports showed that the prevalence of occupational health problems and exposure to occupational health risks were relatively high. Office workers' increased exposure to occupational health problems and risks and other associated adverse health outcomes were attributed to insufficient knowledge of WSC, negative attitude towards WSC, poor practices towards WSC, their work environment and other socio-demographic factors.

The findings thus indicated the need for an intervention to address the high level of exposure to occupational health problems and risks due to poor WSC among administrative workers. Accordingly, five experts from the Faculty of Medicine and Health Sciences, Department of Community Health and Occupational Safety and Health Management Office, Universiti Putra Malaysia, were invited to a meeting to express their views and recommendations on the intervention development.

In the second step, the initial draft of the intervention program module was prepared based on the first meeting with the expert panel. In the third step, the paperwork of the drafted module was presented to the expert panel at the second meeting. In the fourth step, the inputs from the expert panel were again gathered to revise and improve the intervention module. The information motivation and behavior (IMB) model was considered appropriate for the development of program module. The three constructs of the IMB model, namely information, motivation and behaviour, were incorporated into the intervention module.

The intervention program consists of three phases; in phase one, a full-day program was conducted from 9 am until 4 pm, covering a health talk presentation on KAP towards WSC using the IMB model. A health talk presentation on knowledge of WSC was delivered on three topics, definitions and importance of WSC, occupational health risks, and occupational health problems for 3 hours, which addressed the first construct of the IMB model.

The second construct of the IMB model was also discussed by giving a health talk presentation on attitude towards WSC. It covered two topics, the discussion of the attitude towards WSC and the questions and answers of the entire attitude towards WSC questions in the questionnaire for 1 hour. Then, 1 hour was scheduled for lunch break between 1 pm to 2 pm, and the final part of phase one addressed the last construct of the IMB model by giving a health talk presentation on behavioural change approaches in handling occupational health risks and problems towards WSC for 2 hours.

In the second and third phases, after completing the phase one intervention, reminders were sent to the intervention group in phone or WhatsApp messages weekly for three consecutive weeks before the 1 month follow-up data collection and weekly for seven consecutive weeks before the 3 month follow-up data collection for both the phase two and phase three respectively. These reminders served as external cues to promote their practices, reinforce the information and knowledge learned from the intervention program, and encourage them to practice skills learned from the program.

Dependent Variables

This study had three dependent variables: practices towards WSC as the primary outcome, while knowledge and attitudes towards WSC were the secondary outcomes.

Independent Variables

The independent variables were categorised into socio-demography (age, gender, education level and marital status) and occupational/office-related ergonomic factors (work duration per week, working years of experience, knowledge of office ergonomics, using a visual display terminal (VDT) filter or computer screen cover, duration of computer usage, maintaining static position and job title and physical activity).

Study Instrument

The evaluation was done three times using the first formal and locally validated, self-administered WSCQ among the administrative workers. The validation of the WSCQ confirmed high reliability and validity for the evaluation of KAP towards WSC among the study population.22-23 Therefore, the respondents' KAP towards WSC was measured using the WSCQ, first at baseline, second at 1 month, and third at 3 months post-intervention.

Data Analysis

Data obtained were analysed by using the IBM SPSS Statistics 25. Data from the respondents were analysed according to the group to which they were initially randomised. All the numerical data of the dependent and independent variables were not normally distributed, as shown in Tables I and II. Sensitivity analysis which includes per protocol and intention to treat analyses, was adopted to analyse the primary outcome of practice towards WSC in this study, as shown in Table V, and the data loss to follow-up among the respondents at post-intervention was taken into consideration in the analysis.

There were 15 cases reported in this study with a loss of follow-up; a simple imputation method known as the last observation carried forward (LOCF) method was performed in handling the missing data to include all the respondents in the secondary outcomes of knowledge and attitude towards WSC analysis as shown in Table III and IV. In addition, the Chi-square test was used for the bivariate analysis, and Generalized Estimating Equations (GEE) was adopted for the multivariate analysis because GEE is one of the standard statistical techniques used in analysing longitudinal data in clustered trials.

RESULTS

Socio-demographic Characteristics, Occupational/office-related Ergonomic Characteristics, and Outcome Variables Between Research Groups at Baseline

This study showed no significant differences between groups regarding respondents' socio-demographic factors, occupational/office-related ergonomic factors, and the outcomes studied (KAP towards WSC) at baseline. Table I and II show that the distribution and association of socio-demographic factors, occupational/office-related ergonomic factors, and the outcomes studied (KAP towards WSC) in the intervention and waitlist groups were similar at baseline.

Table I: Distribution and association of socio-demographic and occupational/office-related ergonomics characteristics between research groups at baseline

Factors	Research group					
	Intervention (N=122) n (%)	Waitlist (N=125) n (%)	median (IQR)	df	X^2	*p* value
Gender				1	1.006	0.316
Male	46 (37.7)	56 (44.8)				
Female	76 (62.3)	69 (55.2)				
Age group (years)			40.0 (11.0)	1	0.890	0.345
<40	61 (50.0)	71 (56.8)				
>40	61 (50.0)	54 (43.2)				
Educational level				1	0.001	0.977
Degree	90 (73.7)	91 (72.8)				
Others	32 (26.2)	34 (27.2)				
Marital status				1	0.416	0.519
Married	96 (78.7)	93 (74.4)				
Others	26 (21.3)	32 (25.6)				
Duration of work per week			40 (0.0)			
=40	122 (100.0)	125 (100.0)				
Service duration (year)			10 (9.0)	1	0.463	0.496
<10	66 (54.1)	74 (59.2)				
>10	56 (45.9)	51 (40.8)				
Office ergonomic course				1	0.000	1.000
Yes	34 (27.9)	34 (27.2)				
No	88 (72.1)	91 (72.8)				
Job title				1	0.000	1.000
Levels 8, 9, 10 and 12	88 (72.1)	90 (72.0)				
Levels 13, 14, 15, 16 and 17	34 (27.9)	35 (28.0)				
Hours per week work extended			11 (3.0)	1	0.089	0.765
<11	66 (54.1)	71 (56.8)				
>11	56 (45.9)	54 (43.2)				
Maintain a position for a long duration				1	0.003	0.954
Yes	97 (79.5)	98 (78.4)				
No	25 (20.5)	27 (21.6)				
Use computer for long duration				1	0.003	0.954
Yes	97 (79.5)	98 (78.4)				
No	25 (20.5)	27 (21.6)				
Use computer screen cover				1	0.095	0.757
Yes	9 (7.4)	7 (5.6)				
No	113 (92.6)	118 (94.4)				
Take a break for physical activities				1	0.150	0.699
Yes	42 (34.4)	47 (37.6)				
No	80 (65.6)	78 (62.4)				

Notes: Others for single/widow/divorced and master/PhD. Levels 8, 9, 10 and 12 are the following job titles, administrative officer grade II (level 8), administrative officer grade I (level 9), senior administrative officer (level 10) and principal administrative officer (level 12). Levels 13, 14, 15, 16 and 17 are the following job titles, assistant chief administrative officer (level 13), chief administrative officer (level 14), assistant director (level 15), deputy director (level 16) and director (level 17). Statistical test = normality test and Chi-square test, $p<0.05$.

Table II: Distribution and association of KAP towards WSC between research groups at baseline

Factors	Intervention (N=122) n (%)	Waitlist (N=125) n (%)	median (IQR)	df	X^2	*p* value
Knowledge of WSC			207 (9.0)	1	0.745	0.388
<207 (Low)	91 (74.6)	100(80.0)				
>207 (High)	31 (25.4)	25(20.0)				
Attitudes towards WSC			361 (14.0)	1	0.000	1.000
<361 (Negative)	90 (73.8)	93 (74.4)				
>361 (Positive)	32 (26.2)	32 (25.6)				
Practices towards WSC			41 (3.0)	1	0.031	0.860
<41 (Bad)	113 (92.6)	114 (91.2)				
>41 (Good)	9 (7.4)	11 (8.8)				

Statistical test = Normality test and Chi-square test, significant at $p<0.05$

Table III: Effectiveness of intervention on knowledge towards WSC, after adjusting for other factors

Variables	B	SE	Wald	Adjusted OR	95%CI	*p* value
Group						
Intervention	3.462	0.3569	94.110	1.931	2.763, 4.162	0.001*
Control[a]	-	-	-	1	-	-
Time						
3 months post intervention	3.358	0.3223	108.555	1.835	2.726, 3.989	0.001*
1 month post intervention	0.440	0.1201	13.432	1.644	0.509, 0.815	0.001*
Baseline[a]	-	-	-	1	-	-
Gender	0.074	0.2938	0.000	1.005	0.565, 1.787	0.807
Age	0.044	0.4961	0.038	0.908	0.343, 2.400	0.298
Educational level	0.061	0.5584	0.042	0.892	0.299, 2.666	0.913
Marital status	0.454	0.3681	0.550	0.761	0.370, 1.566	0.309
Service duration (year)	-0.036	0.4972	0.186	1.239	0.468, 3.284	0.523
Knowledge of office ergonomic						
No	2.136	0.5145	17.235	1.118	1.127, 3.144	0.001*
Yes[a]	-	-	-	1	-	-
Job title	-1.076	0.6424	2.021	2.492	0.708, 8.777	0.110
Hours per week work extended	0.054	0.3717	0.360	0.800	0.386, 1.658	0.545
Maintain a position for long duration	-0.076	0.3401	0.077	1.099	0.564, 2.141	0.825
Use computer for long duration	-0.076	0.3401	0.077	1.099	0.564,2.141	0.825
Take a break for physical activities						
No	1.678	0.3387	24.526	1.187	1.014, 2.341	0.001*
Yes[a]	-	-	-	1	-	-

Statistical test = GEE, S.E = standard error, CI = confidence interval, [a] reference group, * significant at p<0.05, adjusted for age, gender, educational level, marital status, service duration, attending office ergonomic course, job title, hours per week you work for an extended hour, maintaining a position for a long duration, using the computer for a prolonged duration and taking a break for physical activities.

Table IV: Effectiveness of intervention on attitude towards WSC, after adjusting for other factors

Variables	B	SE	Wald	Adjusted OR	95%CI	*p* value
Group						
Intervention	1.742	0.2503	46.446	1.175	1.251, 1.232	0.001*
Control[a]	-	-	-	1	-	-
Time						
3 months post intervention	2.343	0.2143	119.563	1.096	1.923, 2.763	0.001*
1 month post intervention	1.051	0.1366	59.173	1.350	0.783, 1.319	0.001*
Baselinea	-	-	-	1	-	-
Knowledge of office ergonomic						
No	0.827	0.3399	5.915	1.428	0.160, 1.493	0.015*
Yes[a]	-	-	-	1	-	-
Job title	0.058	0.3070	0.003	0.959	0.539, 1.797	0.858
Hours per week work extended	-0.068	0.2870	1.028	1.338	0.762, 2.348	0.293
Use computer screen cover	0.635	0.4882	1.535	0.546	0.210, 1.422	0.192
Taking a break for physical activities	0.299	0.2706	1.225	0.741	0.436,1.260	0.276

Statistical test = GEE, S.E = standard error, CI = confidence interval, [a] reference group, * significant at *p*<0.05, adjusted for attending office ergonomic course, job title, hours per week you work for an extended hour, using computer screen cover and taking a break for physical activities.

Effectiveness of Intervention on Respondents' Knowledge of WSC

GEE analysis was used to determine the intervention's effectiveness in improving the knowledge of WSC within and between groups from baseline, 1 month, and 3 months post-intervention. Four statistically significant predictors of knowledge were the intervention (*p*<0.001), the time during the intervention (1 month and 3 months post-intervention [p<0.001]), attending an office ergonomic course (*p*<0.001), and taking a break for physical activities (*p*<0.001).

Respondents who received the WSCHEM were more likely to improve their knowledge of WSC than those in the waitlist group after adjusting for the clustering effect and other factors (AOR=1.93, 95%CI 2.76 4.16), as shown in Table III.

Effectiveness of Intervention on Respondents' Attitudes of WSC

GEE analysis was used to determine the effectiveness of the intervention in improving attitudes towards WSC within and between groups from baseline, 1 month, and 3 months post-intervention. There were three statistically significant predictors of knowledge, first, the intervention (p<0.001), the time during the intervention (1 month and 3 months post-intervention (*p*<0.001)), and attending an office ergonomic course (*p*<0.001).

Respondents who received the WSCHEM were more likely to improve their attitude towards work safety culture than those in the waitlist group after adjusting for the clustering effect and other factors (AOR=1.18, 95%CI 1.25 2.23), as shown in Table IV.

Effectiveness of Intervention on Respondents' Practices of WSC

Sensitivity analysis was conducted for the primary outcome of practices towards WSC to examine the robustness of the findings through the per-protocol analysis and intention-to-treat analysis. As shown in Table V, the GEE results showed

Table V: Per-protocol/intention to treat analysis on the effectiveness of the intervention on practices towards WSC, after adjusting for other factors

Variables	B	SE	Wald	Adjusted OR	95%CI	*p* value
Group						
Intervention	6.788	0.9875	47.253	1.821	4.852, 8.723	0.001*
Control[a]	-	-	-	1	-	-
Time						
3 months post intervention	6.218	0.8798	49.924	1.702	4.493, 7.942	0.001*
1 month post intervention	-0.098	0.0798	1.501	1.103	0.943, 1.289	0.221
Baseline[a]	-	-	-	1	-	-
Interaction						
Intervention x 3 months	7.020	1.0531	44.445	1.971	4.956, 9.084	0.001*
Intervention x 1 month	7.202	1.0537	46.722	1.971	5.137, 9.268	0.001*
Intervention x baseline[a]	-	-	-	-	-	-
Waitlist x 3 months[a]	-	-	-	-	-	-
Waitlist x 1 month[a]	-	-	-	-	-	-
Waitlist x baseline[a]	-	-	-	-	-	-
Maintain a position for long duration						
No	-2.526	0.6008	17.683	12.507	3.853, 40.603	0.001*
Yes[a]	-	-	-	1	-	-
Use computer for long Duration						
No	-2.526	0.6008	17.683	12.507	3.853, 40.603	0.001*
Yes[a]	-	-	-	1	-	-
Use computer screen cover						
No	3.452	0.9125	14.309	0.832	1.663, 5.240	0.001*
Yes[a]	-	-	-	1	-	-
Take a break for physical activities						
No	2.674	0.5739	21.704	1.069	1.549, 3.798	0.001*
Yes[a]	-	-	-	1	-	-

Statistical test = GEE, S.E = standard error, CI = confidence interval, [a] reference group, * significant at $p<0.05$, adjusted for maintaining a position for a long duration, using the computer for a prolonged duration, using computer screen cover, and taking a break for physical activities.

that there were six significant predictors for practices towards WSC: the intervention ($p<0.001$), time at 3 months post-intervention ($p<0.001$), maintaining a position for a long duration ($p<0.001$), using the computer for a prolonged duration ($p<0.001$), using computer screen cover ($p<0.001$) and taking a break for physical activities ($p<0.001$).

The per-protocol analysis findings were comparable to the intention-to-treat analysis in which the respondents from the intervention group were 1.821 times more likely to improve their practices towards the work safety culture ($p<0.001$) than those in the waitlist group after adjusting for other factors.

The intention-to-treat analysis included the interaction term between the group and the time point. The results in Table V showed that the time point ($p<0.001$) at 3 months post-intervention and the interaction term of group and time point ($p<0.001$) were the significant predictors of practices towards WSC. Furthermore, the interaction showed a significant association (B = 7.020, 95%CI = 4.956, 9.084) with practices towards WSC.

DISCUSSION

Research Groups' Differences in the Respondents at Baseline

There were no significant differences between intervention and waitlist groups regarding respondents' socio-demographic characteristics and occupational/office-related ergonomics characteristics at baseline. Also, there was no significant difference between the intervention and waitlist groups in terms of the outcomes studied KAP towards WSC. The comparable findings at baseline showed that the simple randomisation process was appropriately conducted to minimise the possible covariates between groups.

Changes in Knowledge of WSC Among the Respondents

The results show that the intervention effectively increased the knowledge of WSC. Respondents in the intervention group showed a significant increase in knowledge of WSC compared to the waitlist group. This finding was similar to another study in Denmark.[24] In that study, the intervention effectively reduced short-term sickness absence due to high knowledge of WSC among respondents in the intervention group after the program (ARR 0.84 95% Cl 0.69 1.01) compared to the control group. In addition, another study in Turkey on burnout levels and job satisfaction of hospital office workers showed that intervention in the form of training effectively decreased burnout levels due to high knowledge of WSC among the respondents after the training ($p<0.05$).[25]

Another factor that had a statistically significant association with knowledge of WSC was office ergonomics knowledge. The intervention was effective to increased knowledge of office ergonomics among the respondents. This finding is similar to the study conducted in China on knowledge of WSC to assess the effect of ergonomic training on awareness of work-related musculoskeletal disorders among teachers in China.[26] After the intervention, the awareness rate improved. The study showed a significant ($p<0.05$) decrease in the

prevalence of work-related musculoskeletal disorders due to high knowledge of WSC among the respondents after the intervention. The similar study showed a decrease in the prevalence of metabolic syndrome (MetS) among those respondents who attended an office ergonomic course due to their high knowledge of WSC.[27] Attending office ergonomic courses (ORD 1.26, 95% CI: 1.02–1.56) was significantly associated with a decrease in the prevalence of MetS.

Taking a break for physical activities had a significant association with knowledge of workplace safety culture. The intervention effectively increased knowledge of physical activities to reduce occupational health risks among administrative workers. This finding is studied in similar study on knowledge of WSC regarding factors associated with physiological stress among office workers in the United States.[28] Higher physical activity at the office was significantly related to lower levels of physiological stress (B=−26.12 ms/mG; 95% CI−40.48 to −4.16) among the office workers.

Changes in Attitudes Towards WSC Among the Respondents
The intervention effectively increased the attitude towards WSC. Respondents in the intervention group showed a significant increase in attitude towards WSC compared to the waitlist group. Similar to this finding was another study by Sanaeinasab et al[29] on attitudes towards work safety intervention to determine the effectiveness of a model-based health education intervention to improve ergonomic posture, in-office computer workers. There were significant differences in the Rapid Office Strain Assessment (ROSA) between the intervention group and control group at follow-up ($p<0.05$). The mean ROSA score decreased from 5.65 (SD 1.03) to 3.95 (SD 0.83) in the intervention group, while no significant change was found in the control group.

Another factor that had a statistically significant association with a positive attitude towards WSC was knowledge of office ergonomics. Therefore, the intervention effectively increased knowledge of office ergonomics among the respondents. Another study showed similar findings; the study was on attitudes towards WSC regarding the prevalence of low back pain (LBP) among office workers in a public university in Malaysia.[30] The study showed a decrease in the prevalence of LBP due to their positive attitude towards WSC among those respondents who attended office ergonomics courses. On the other hand, LBP was high among those respondents who did not participate in the office ergonomics course (91.2%).

Changes in Practices Towards WSC Among the Respondents
In terms of the effectiveness of the intervention on practices towards WSC for the per-protocol/intention to treat analysis, respondents from the intervention group showed statistically significant improvement in the practices of good WSC compared to the waitlist group. This finding was similar to another study in Germany, Denmark, and Austria.[31] In that study, the intervention effectively improved work stress management among the intervention group (Man GO) due to their good practices towards WSC compared to the control group. In addition, the study showed a significant ($p<0.001$) improvement in work stress after the intervention. In another study conducted in Malaysia, the USA, and Iran, it was observed that the intervention effectively decreased neck, shoulders and LBP among the intervention group due to their good practices towards WSC with a significant ($p<0.05$) reduction in the neck, shoulders and LBP among the exercise group (intervention group) compared to the control group.[32]

Maintaining a position for a long duration or using the computer for a prolonged period had a significant association with practices towards WSC. The intervention effectively improved the respondents' practice towards work safety regarding the occupational risk of prolonged sitting or prolonged duration of computer usage at work that is more than 6 hours per day and without taking a break every 2 working hours. This finding is similar to the study conducted by Bawa et al[33] on practices towards WSC regarding the prevalence of LBP among middle-aged office workers in the Lebanese population. The study showed a decrease in LBP due to good practices towards WSC among the respondents who do not maintain a prolonged static position at work. The logistic regression showed that LBP was positively associated with maintaining the same posture for > 5 hours ($p=0.024$); maintaining the same posture for 5 hours or more is three times riskier of LBP (OR= 3.648, 95%CI:1.183; 11.253. Also, the study conducted by Kaliniene et al34 on practices towards WSC regarding the prevalence rates of shoulder, elbow, wrist/hand, upper and LBP among computer workers of the public sector in Lithuania. The study showed an increase in the prevalence of shoulder pain due to bad practices towards WSC among the respondents who maintain a prolonged static position when using a computer at the workplace. The duration of working with a computer was found as a significant factor for shoulder pain. The majority of the respondents estimated that they worked with a computer for more than 6 hours per day and did not have a break every 2 working hours.

This study also showed that using computer screen covers had a significant association with practices towards WSC. The intervention effectively improved the respondents' practices towards work safety culture regarding the use of computer screen covers or visual display terminals (VDT) when working with computers at work. This finding is similar to the study on practices towards WSC to assess the prevalence of computer vision syndrome (CVS) among computer office workers in Sri Lanka.[35] The study showed an increase in the prevalence of CVS due to bad practices towards WSC among the respondents who do not use computer screen covers at the workplace. Binary logistic analysis showed that not using a VDT filter (OR: 1.02; 95%CI: 1.01, 1.03) was significantly ($p<0.01$) associated with the presence of CVS. Also, a study on practices towards WSC to assess the prevalence and associated risk factors of CVS among the computer science students of an engineering college of Bengaluru in India.[36] The study showed an increase in the prevalence of CVS due to the bad practices towards WSC among the respondents who do not use computer screen covers at the workplace. Chi-square analysis showed the association between CVS and screen having glare filter was found to be statistically significant ($p<0.001$), with 91.8% of the students who do not use computer screen cover having CVS.

Taking a break for physical activities had a significant association with practices towards WSC. The intervention effectively increased the respondents' good practices in the

use of physical activities to reduce occupational health risks among the administrative workers. This finding is similar to the study done by [37] in Australia on practices towards WSC to evaluate the effects of 12 weeks of combined ergonomics and neck/shoulder strengthening exercise intervention (EET) and 12 weeks of combined ergonomics and health promotion intervention (EHP) on work ability among office workers. The intervention effectively increased the work ability among the intervention group respondents (EET) due to their good practices towards WSC. In addition, a significant group by time interaction effect at 12 weeks (p=0.03) and a near significant at 12 months (p=0.06) favoured the EET group (intervention group) in the per-protocol analysis of the neck cases with ≥70% adherence to the intervention compared to the EHP group (control group). Also, another study conducted on practices towards WSC among office workers in Canada to assess whether completing practical exercises is associated with improved well-being compared with reading information modules.[38] This study showed that office workers who preferred practical exercises over information modules had 2.22 times greater odds of reporting improved well-being from the web-based health intervention (P=.01; 95% CI 1.20-4.11).

The single blinding technique was planned but it was challenging to apply as the respondents could differentiate the module used for either intervention or waitlist group based on the respondent's information sheet received before the randomisation process. In addition, this study also limited the findings' generalisability to the administrative workers (AW) as a whole in Nigeria, as it was conducted only in one district among administrative workers from 20 ministries (clusters) at the civil service office complex in Abeokuta.

CONCLUSION

The intervention, WSCHEM, was effective in improving the administrative workers' KAP towards WSC, as demonstrated by the significance between and within-group differences. However, more time points for evaluation are recommended to check the sustainability of the desired behaviour health outcomes (KAP towards WSC).

ETHICS STATEMENT

Ethical clearance was first obtained from the Universiti Putra Malaysia Ethics Committee for Research Involving Human Subjects (JKEUPM) with reference number JKEUPM-2020-051. Then, permission to conduct the study at the study location was obtained from the head of the service, Abeokuta, Ogun State, in Nigeria.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. Anisah Baharom and Assoc. Prof. Dr. Rosliza Abdul Manaf for their permission to conduct this study after UPM ethical committee review. In addition, I wish to thank my supervisor Dr. Titi Rahmawati binti Hamedon, and my co-supervisors, Dr. Aidalina binti Mahmud and Assoc. Prof. Dr. Mohd Rafee bin Baharudin for their constructive suggestions and corrections in the preparation, conduct, writing, and submission of the manuscript.

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ORIGINAL ARTICLE

Factors associated with the usage of health insurance among cancer patients in public hospitals in a middle-income country

Sharifa Ezat Wan Puteh, PhD, Yang Rashidi Abdullah, MSc, Azimatun Noor Aizuddin, PhD

Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Bangi, Malaysia

ABSTRACT

Introduction: Private health insurance (PHI) plays an important supplementary role on top of the existing subsidised health financing system to prevent heavy reliance on out-of-pocket (OOP) expenses, especially in diseases with high costly treatment. This study was done to examine the factors associated with PHI usage among cancer patients and its associated influencing factors in Malaysia.

Materials and Methods: This cross-sectional study was conducted in three Malaysian public hospitals using a multi-level sampling technique to recruit 630 respondents. A validated self-developed four-domain questionnaire which includes one domain for health insurance was used to collect the relevant data.

Results: Approximately 31.7% of the respondents owned PHI. The PHI usage was significantly higher among male respondents (p=0.035), those aged 18–40 years old (p<0.001), Indian and Chinese ethnicities (p=0.002), with tertiary education level (p<0.001), employed (p<0.001), working in the private sector (p<0.001), high household income (T20) (p<0.001), home near to the hospital (p=0.001) and medium household size (p<0.001). The significant predictive factors were age 18–40 years aOR 3.01 (95% CI: 1.67–5.41), age 41–60 years aOR 2.22 (95% CI 1.41–3.49), medium (M40) income aOR 2.90 (95% CI: 1.92–4.39) and high (T20) income aOR 3.86 (95% CI: 1.68–18.91), home near to the hospital aOR 1.68 (95% CI: 1.10–2.55), medium household size aOR 2.20 (95% CI: 1.30–3.72) and female head of household aOR 1.79 (95% CI: 1.01–3.16). The type of cancer treatment, the location of treatment, prior treatment in private healthcare facilities and existence of financial coping mechanisms also were significant factors in determining PHI usage among cancer patients in this study.

Conclusion: Several factors are significantly associated with PHI usage in cancer patients. The outcome of this study can guide policymakers to identify high-risk groups which need supplementary health insurance to bear the cost for their cancer treatment so that a better pre-payment health financing system such as a national health insurance can be formulated to cater for these groups.

KEYWORDS:
Health insurance, Health insurance in cancer, Health insurance in Malaysia

INTRODUCTION

Insurance is a promise of compensation for specific potential future losses in exchange for a periodic payment.[1] There are many types of insurance schemes available, namely life insurance, medical/health insurance, automobile insurance, property insurance and disability insurance. Health insurance is a programme designed to cover against critical illness occurrences, hospitalisation, medical, surgical, accident and other health risks expenses that are incurred by the insured (person covered). It is a critical pillar of health care financing and the main driver in achieving UHC in most nations. Health insurance provides financial access care and helps to protect the populations against high treatment cost. Moreover, health insurance protects households against large out-of-pocket expenses resulting from catastrophic illnesses.

Typically, insurance is voluntarily purchased by individuals, who pay different premiums depending on the type of health insurance and the level of coverage. Health insurance can either reimburse the insured for expenses incurred from illness or injury or pay to the healthcare provider directly (e.g. hospitals). Health insurance concept is to create a pool of fund through contributions made by individual who seeks for protection. Basically, this risk-sharing concept is a contract between the insured and the insurance provider, whereby the insurance companies will act as a trustee and if any person suffers a loss, the insurer will compensate out the contribution from the pool of fund.[2]

Malaysia is an upper-middle-income country that adopts the provision of subsidised public health services to all citizens through national taxation.[3] Primary care at public health clinics costs only USD0.24, which includes medication.[4] The Ministry of Health Malaysia (MOH) reported the country's total health expenditure (THE) for 2019 was RM64.3 billion or 4.3% of gross domestic product (GDP).[5] The per capita expenditure on health was RM1974. Public sources of financing remained higher than private, with public sector contributing 52.5%, while private source of financing was 47.5%. The MOH expenditure on health was the highest source of funding with 44.9% of THE, followed by out-of-pocket (OOP) expenditure with 35% of THE. The highest health expenditure was in hospitals at RM35.5 billion or 55% of THE followed by ambulatory care providers.

The expenditure on health care in Malaysia has been increasing over the years and it brings a challenge not only for the Malaysian population, but also to the government

This article was accepted: 18 May 2023
Corresponding Author: Yang Rashidi Abdullah
Email: dr.yrashidi@moh.gov.my/kid_creole71@yahoo.com

and the insurance providers. With the rising cost of healthcare, it has increased the demand and expectation on health financial providers. The reasons for increase in the medical costs are the increase in the communicable and non-communicable diseases, the ageing population and the effects of globalisation where diseases can be transmitted to different countries within a short period of time. Furthermore, newer and better medications and treatment modalities will be expensive and with these improved treatment sciences, many diseases can be treatable and curable. Consequently, these increasing trends of health care expenditure will simultaneously increase the out-of-pocket expenditure.

The public health system is currently overburdened and underfunded with some of the more expensive treatments that need to be paid for by the patients.[6] This in the long run can overburden the government and subsequently heavy reliance on out-of-pocket expenditures expenses due to the additional costs of treatment, which are not covered or partially covered by the subsidised system may lead to catastrophic health costs and a decline in individual economic status. However, given that health reform by adopting a national health insurance is currently not yet implemented in Malaysia due to various reasons, some patients need to be supplemented through a voluntary pre-payment scheme like PHI, on top of the existing subsidised health financing through the national taxation, to prevent heavy reliance on OOP. Through these roles, PHI also allows greater access to private health care that offers preferential choice for timely care, provider, care options and waiting time, which may contribute towards health and well-being.[7]

The latest available data reported the proportion of PHI uptake in Malaysia at 22% in 2019.[8] This proportion is considerably high when compared to China and Brazil, which reported lower proportions of PHI coverage of 5.0% and 13%, respectively.[9,10] It is important to note, however, that the health financing mechanisms in both countries were dominated by mandatory health insurance schemes, which serve little need for voluntary PHI purchasing. There are also instances for examples in France where the PHI coverage was as high as 86% because the statutory health insurance only covers up to 75% of THEs, thus the complementary PHI is required to reimburse co-payments and medical products or services not covered by the public healthcare system.[11]

In spite of all this, a mandatory social health insurance has not been implemented in Malaysia, although the planning for it has been in the process for many years. Although the government has introduced Peka B40 dan MySalam health subsidy initiatives to lower income groups, both initiatives are not equivalent to the PHI and the preferential access benefit that it offers. Additionally, the PHI coverage in Malaysia is still low, and the cause of PHI insufficiency is probably due to lack of knowledge regarding the importance of PHI and feeling unaffordable to purchase PHI because the premiums can vary greatly depending on the extent and duration of coverage. And since PHI is risk-rated, increasing age or individuals with pre-existing conditions may either be charged higher premiums or precluded from purchase.[12] The report produced by the Central Bank of Malaysia in 2017 showed the uptake of insurance and *takaful* was low among the population from bottom 40% of household income category (B40) as compared to the national population.[13] With the PHI premiums set to be at least MYR200 (USD51) yearly and continues to increase rapidly,[14] lower income group is less willing and able to pay premiums.

Cancer is among the leading causes of morbidity and mortality worldwide. The number of new cancer cases in Malaysia is around 48,639 in 2020 and these numbers increase significantly within the ageing population, those living unhealthy lifestyles and those with exposure to carcinogens substances.[15] Often times, public health system requires longer waiting periods for receiving treatment. The opportunity to return to health is higher and the probability of death can be reduced in a disease like cancer if the patients can receive treatment as soon as possible. For example, a chance to recover for Stage I cancer is between 90% and 95%, while the opportunity to cure Stage IV cancers is only about 15%. Hence, many people will choose the private health system to seek the best possible treatment, although the cost of private health spending is more expensive.[16]

The purpose of this paper was to examine the factors associated with PHI ownership and usage among cancer patients in Malaysia. This study also highlights the prevalence of PHI among the cancer patients in an attempt to help inform policymakers and researchers to pay attention to PHI and the role it can play in the public–private healthcare systems partnerships. It is hoped that inferences from the study can guide policymakers to identify high-risk groups which need supplementary health insurance to bear the cost for their cancer treatment so that a better pre-payment health financing system such as a national health insurance can be formulated to cater for these groups. By determining which factors most influence individuals' health insurance purchase decisions, it can be instrumental in offering new information for the policymakers to design more effective programs for patients who need health insurance.

MATERIALS AND METHODS

The study was conducted in three public hospitals with oncology services in Malaysia, namely National Cancer Institute (NCI), Hospital Kuala Lumpur (HKL) and Hospital Canselor Tuanku Muhriz (HCTM), all located in Klang Valley (KV), central region West Malaysia, in which 30% of cancer cases in Malaysia are treated.17 The three hospitals under the study are national referral centres for cancer cases from all over the country and they all have radiotherapy and oncology departments that provide radical and palliative treatments to cancer patients in the country.

This is a cross-sectional study conducted from February 2020 to February 2021. The sampling in this quantitative research was done using multi-level sampling methods, whereby the hospital was chosen using convenient sampling. This was followed by purposive sampling of the oncology department, universal sampling of patients at the inpatient and outpatient services of the oncology department, and subsequently systematic sampling of patients at the department.

The total number of samples from all three hospitals calculated using the Lwanga dan Lemeshow (1991) formula to calculate sample size for two proportions was 630. The total number of samples was distributed equally among the three hospitals making the number of samples included in this study from each hospital to be 210. The inpatient and outpatient samples were distributed equally. The ward admission lists and clinic/day-care/radiotherapy clinic attendance lists were used as a basis to recruit the inpatient and outpatient samples in the department. Informed consent was obtained from the respondents, confidentiality re-assured. Ethical clearance was received from the Malaysian Research Ethical Committee and permission to conduct data collection was approved by the hospital directors.

A self-developed questionnaire and document review of the patient's case notes and hospital documents were the study tools used in this study. The questionnaire consisted of four domains, namely the demographic and socio-economic domain, the disease and treatment domain, the health financing domain and the health insurance domain. The questionnaire was validated using content and face validity, whereby the content validation of the questionnaire was conducted by doing literature reviews on research papers/journals/books related to this study to ensure all the important and associated PHI factors were included in this study, and then inputs from two health economists and a cancer institute deputy director were taken.

Face validation was then conducted whereby pre-testing of the questionnaire on 20 respondents who were not part of the study sample was done to make sure the sentences and questions in the questionnaire were understood by the respondents. Family members that took care of the patients and the hospital staff in-charge of the cancer patients were also interviewed when necessary to get additional data. All the sources of household income and household expenses including the health expenses were accounted for in the questionnaire. All income and expenditure were reported in Malaysian currency RM (RM1 = USD0.24).

The inclusion criteria were Malaysian citizen, aged 18 and above, with any types or stages of cancer. Patients who did not give consent, mentally unstable, unconscious or unable to communicate were excluded from this study. The household income groups were categorised into lower income (B40), middle income (M40) and high income (T20) groups according to the household income expenditure. Home distance from the hospital was categorised into within Klang Valley (near to hospital) and outside Klang Valley (far from hospital). The household size was categorised into 1–2 members (small size), 3–5 members (medium size) and more than five members (large size).

The types of cancer were categorised according to their primary location in the body. The cancer duration was divided into less than 1 year (short duration), 1–2 years (moderate duration) and more than 2 years (long duration). The cancer stage was categorised into Stage I to Stage IV based on the existing cancer staging criteria. The types of treatment were categorised into symptomatic/follow-up treatment, chemotherapy, radiotherapy and a combination of chemo-radiotherapy treatments. The frequency of treatment per year was divided into 1–3 (infrequent), 4–11 (frequent) and 12 sessions or more (very frequent). Guarantee Letter (GL) is a document provided by an employer or insurer for a patient to obtain a waiver of the treatment payment required by the hospital. Health financial aid is defined as any financial assistance or contribution in the form of monetary assistance, payment guarantees, cost-sharing arrangements, subsidies or welfare payments from family, friends, government organisations or non-governmental organisations which is specific for the purpose of paying for healthcare.

Respondents were asked to state how much health insurance premium they were paying per month, and these were divided into less than RM100, RM100 to RM250, RM251 to RM500 and more than RM500. As a social health insurance is not available yet in Malaysia, private health insurance (PHI) was studied in this paper. PHI type was categorised into individual purchase and employer-sponsored health insurance. Types of location covered were divided into inpatient only, outpatient only and both inpatient and outpatient services. Type of health services covered were either for all types of services (including for surgery) or not. Those without health insurance were put into the "Not applicable" category.

The data were analysed using Statistical Package for Social Sciences (SPSS 22.0) version 22.0 software. The descriptive analysis was done using frequency distribution, central tendency and variability of a data set, while the bivariate analysis was done using the two-sided chi-square test, followed by multivariate analysis using binomial logistic regression. The fit of the logistic regression model was tested using Omnibus, Hosmer and Lemeshow and Nagelkerke R-Squared tests.

RESULTS

Numerical Data Analysis

The mean age of the respondents was 54.25 years old (SD ±12.52), and the mean household size was 4.1 (SD ±1.84). Table I reveals the mean, median, standard deviation and inter-quartile (IQR) values of the age, household size, income and expenditures of the respondents. The monthly median income, household expenditure and healthcare expenditure were RM3320 (IQR = 3500), RM2587 (IQR = 2466) and RM350 (IQR = 441), respectively (RM1 = USD0.24).

PHI Analysis

According to the findings in Table II, only 31.7% of the respondents in this study have PHI, while majority (68.3%) did not have PHI. Majority of the respondents with PHI indicated that they pay RM100 to RM250 per month for the insurance premium, 7.1% pay RM251 to RM500 per month, 4.1% pay less than RM100 per month while 2.4% pay more than RM500 per month. The percentage of having individual purchase PHI was slightly higher (17.8%) compared to employer-sponsored PHI (14.0%).

Majority (27.6%) of the respondents with PHI were covered for both inpatient and outpatient services, while coverage for

Table I: Numerical data analysis of the respondents

				Interquartile range		
	Mean	Median	SD	25th	50th	75th
Age	54.25	56.00	12.52	46.00	56.0	64.00
Household size	4.1	4.0	1.84	3.0	4.0	5.0
Monthly income (RM)	4369	3320	3652	2000	3320	5500
Monthly expenditure (RM)	3136	2587	2316	1578	2587	4044
Monthly health expenditure (RM)	557	350	758	200	350	641

* RM1 = USD0.24
SD = standard deviation.

Table II: Private health insurance (PHI) analysis (n = 630)

	Frequency	Percentage
Presence of PHI		
Yes	200	31.7
No	430	68.3
Amount of monthly premium		
< RM100	26	4.1
RM100–RM250	114	18.1
RM251–RM500	45	7.1
> RM500	15	2.4
Not applicable	430	68.3
Type of PHI		
Individual purchase	112	17.8
Employer sponsored	88	14.0
Not applicable	430	68.3
Types of location		
Inpatient only	18	2.9
Outpatient only	8	1.3
Both inpatient and outpatient	174	27.6
Not applicable	430	68.3
Types of health services		
All services	67	10.6
Certain services only	133	21.1
Not applicable	430	68.3

* Average monthly insurance premium = RM263.28
Monthly insurance premium = minimum RM30 ; maximum RM3300

inpatient only and outpatient only were much less (2.9% and 1.3%). In addition, 21.1% of the respondents with PHI were covered for certain health services only while 10.6% were covered for all health services including surgery. The study also found the average monthly health insurance premium was RM263.28, whereby the minimum and maximum amount of the monthly insurance premium was RM30 and RM3300, respectively.

Descriptive and Bivariate Analysis

The descriptive analysis in Table III shows that the majority of the respondents were female (72.2%), aged 41–60 years old (51.6%), Malay ethnicity (69.7%), married (76.0%), had secondary school education (50.8%), unemployed (51.1%), other employment sector (73.3%), lower income group (65.2%), home near the hospital (62.9%), from urban areas (82.9%), not a single parent (86.0%), medium household size (58.9%), had male as head of household (87.1%), cancer duration less than 1 year (51.3%), outpatient treatment location (72.7%), without surgery (53.8%), without prior treatment in private healthcare facilities (87.9%), with other chronic diseases (52.9%), without disability (93.8%), frequent treatment (51.9%), without GL (60.2%), without financial health aides (93.2%) and with financial coping mechanism (58.4%).

The bivariate analysis in Table III shows that health insurance was significantly higher in the groups with male respondents (p=0.035), those aged 18–40 years old (p< 0.001), Indian and Chinese ethnicities (p=0.002), tertiary education level (p<0.001), employed (p<0.001), working in the private sector (p<0.001), high household income (T20) (p<0.001), home near to the hospital (p=0.001), medium household size (p<0.001), undergoing combination chemo-radiotherapy (p=0.022), inpatient treatment location (p<0.001), without treatment in private healthcare facility (p<0.001) and with financial coping mechanism (p<0.001).

Logistic Regression Analysis

The logistic regression analysis in Table IV shows the results were significant in the groups with respondent age 18–40 years aOR 3.01 (95% CI 1.67–5.41), age 41–60 years aOR 2.22 (95% CI 1.41–3.49), M40 income aOR 2.90 (95% CI 1.92 – 4.39), T20 income aOR 3.86 (95% CI 1.68–18.91), within Klang Valley (home near to hospital) aOR 1.68 (95% CI 1.10–2.55), medium household size aOR 2.20 (95% CI 1.30–3.72), female head of household aOR 1.79 (95% CI 1.01–3.16), follow-up/symptomatic treatment aOR 5.56 (95% CI 1.73–17.89), chemotherapy treatment aOR 4.40 (95% CI 1.40–13.82), radiotherapy treatment aOR 6.82 (95% CI 2.07–22.47), outpatient treatment location aOR 1.97 (95% CI 1.21–3.19), prior treatment in private healthcare facilities aOR

Table III: Descriptive and bivariate analysis of study population

	Descriptive Analysis	Bivariate Analysis Health insurance		*p* value
		Yes	No	
	n (%)	n (%)	n (%)	
Gender				**0.035***
Male	175 (27.8)	77 (44.0)	98 (56.0)	
Female	455 (72.2)	159 (34.9)	296 (65.1)	
Age				**< 0.001***
18–40	99 (15.7)	49 (49.5)	50 (50.5)	
41–60	325 (51.6)	137 (42.2)	188 (57.8)	
> 60	206 (32.7)	50 (24.3)	156 (75.7)	
Ethnicity				**0.002***
Malay	439 (69.7)	145 (33.0)	294 (67.0)	
Chinese	106 (16.8)	52 (49.1)	54 (50.9)	
Indian	73 (11.6)	36 (49.3)	37 (50.7)	
Others	12 (1.9)	3 (25.0)	9 (75.0)	
Marital status				0.876
Single	52 (8.3)	19 (36.5)	33 (63.5)	
Married	479 (76.0)	182 (38.0)	297 (62.0)	
Divorced/ Widowed	99 (15.7)	35 (35.4)	64 (64.6)	
Education level				**< 0.001***
None	18 (2.9)	7 (38.9)	11 (61.1)	
Primary school	109 (17.3)	28 (25.7)	81 (74.3)	
Secondary school	320 (50.8)	96 (30.0)	224 (70.0)	
College/University	183 (29.0)	105 (57.4)	78 (42.6)	
Employment status				**< 0.001***
Employed	164 (26.0)	91 (55.5)	73 (44.5)	
Self-employed	38 (6.0)	15 (39.5)	23 (60.5)	
Retired/Pensioner	106 (16.8)	31 (29.2)	75 (70.8)	
Unemployed	322 (51.1)	99 (30.7)	223 (69.3)	
Employment sector				**< 0.001***
Government	69 (11.0)	37 (53.6)	32 (46.4)	
Private	99 (15.7)	56 (56.6)	43 (43.4)	
Others	462 (73.3)	143 (31.0)	319 (69.0)	
Household income				**< 0.001***
B40	411 (65.2)	109 (26.5)	302 (73.5)	
M40	183 (29.0)	101 (55.8)	80 (44.2)	
T20	36 (5.7)	26 (68.4)	12 (31.6)	
Home distance from hospital				**0.001***
Near (within Klang Valley)	396 (62.9)	167 (42.2)	229 (57.8)	
Far (outside Klang Valley)	234 (37.1)	69 (29.5)	165 (70.5)	
Home area				0.065
Rural	108 (17.1)	32 (29.6)	76 (70.4)	
Urban	522 (82.9)	204 (39.1)	318 (60.9)	
Single parent household				0.641
Yes	88 (14.0)	31 (35.2)	57 (64.8)	
No	542 (86.0)	205 (37.8)	337 (62.2)	
Household size				**< 0.001***
1-2 (small)	134 (21.3)	28 (21.1)	105 (78.9)	
3-6 (medium)	371 (58.9)	183 (42.1)	252 (57.9)	
> 6 (large)	125 (19.8)	25 (40.3)	37 (59.7)	
Head of household gender				0.164
Male	549 (87.1)	200 (36.4)	349 (63.6)	
Female	81 (12.9)	36 (44.4)	45 (55.6)	
Type of cancer				0.389
Head and neck	59 (9.4)	36 (61.0)	23 (39.0)	
Breasts	247 (39.2)	153 (61.9)	94 (38.1)	
Lungs	49 (7.8)	24 (49.0)	25 (51.0)	
Gastrointestinal	120 (19.0)	79 (65.8)	41 (34.2)	
Genitourinary	92 (14.6)	61 (66.3)	31 (33.7)	
Others	63 (10.0)	41 (65.1)	22 (34.9)	
Cancer duration				0.096
< 1 year	323 (51.3)	194 (60.1)	129 (39.9)	
1 to 2 years	123 (19.5)	73 (59.3)	50 (40.7)	
> 2 years	184 (29.2)	127 (69.0)	57 (31.0)	
Cancer staging				0.063
Stage I	67 (10.6)	35 (52.2)	32 (47.8)	
Stage II	145 (23.0)	87 (60.0)	58 (40.0)	
Stage III	218 (34.6)	150 (68.8)	68 (31.2)	
Stage IV	200 (31.7)	122 (61.0)	78 (39.0)	

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Table III: Effectiveness of intervention on knowledge towards WSC, after adjusting for other factors

	Descriptive Analysis	Bivariate Analysis Health insurance		*p* value
	n (%)	Yes n (%)	No n (%)	
Current cancer treatment				**0.022***
Follow-up/Symptomatic	186 (29.5)	111 (59.7)	75 (40.3)	
Chemotherapy	281 (44.6)	176 (62.6)	105 (37.4)	
Radiotherapy	127 (20.2)	76 (59.8)	51 (40.2)	
Chemo-radiotherapy	36 (5.7)	31 (86.1)	5 (13.9)	
Treatment location				**< 0.001***
Inpatient	172 (27.3)	132 (76.7)	40 (23.3)	
Outpatient	458 (72.7)	262 (57.2)	196 (42.8)	
Surgery				0.099
Yes	291 (46.2)	172 (59.1)	119 (40.9)	
No	339 (53.8)	222 (65.5)	117 (34.5)	
Prior treatment in private healthcare facilities				**< 0.001***
Yes	76 (12.1)	20 (26.3)	56 (73.7)	
No	554 (87.9)	374 (67.5)	180 (32.5)	
Other chronic diseases				0.434
Yes	333 (52.9)	213 (64.0)	120 (36.0)	
No	297 (47.1)	181 (60.9)	116 (39.1)	
Disability				0.373
Yes	39 (6.2)	27 (69.2)	12 (30.8)	
No	591 (93.8)	367 (62.1)	224 (37.9)	
Treatment frequency (per year)				0.234
1–3 times (not frequent)	61 (9.7)	44 (72.1)	17 (27.9)	
4–11 times (frequent)	327 (51.9)	204 (62.4)	123 (37.6)	
≥ 12 times (very frequent)	242 (38.4)	146 (60.3)	96 (39.7)	
Guarantee Letter (GL)				0.398
Yes	251 (39.8)	162 (64.5)	89 (35.5)	
No	379 (60.2)	232 (61.2)	147 (38.8)	
Health financial aides				0.310
Yes	43 (6.8)	30 (69.8)	13 (30.2)	
No	587 (93.2)	364 (62.0)	223 (38.0)	
Financial coping mechanism				**< 0.001***
Yes	368 58.4)	269 (73.1)	99 (26.9)	
No	262 (41.6)	125 (47.7)	137 (52.3)	

*Significant results.

4.81 (95% CI 2.57–9.00) and without financial coping mechanism aOR 2.53 (95% CI 1.72–3.73). The final model for logistic regression had a good fit with Omnibus test result of $p<0.001$, Hosmer & Lemeshow test result of $p=0.140$ and the Nagelkerke R2 value was 0.50.

DISCUSSION

Our study found 31.7% of the respondents have PHI coverage, which was higher than the national data of 22% in the 2019 National Health Morbidity Survey (NHMS).[8] This is probably due to the higher need for PHI in cancer patients to supplement the payment for their more costly cancer treatment, as not all cancer treatments in public hospitals are fully subsidised by the government. Although Malaysia introduced measures such as personal income tax relief and stand-alone sale of insurance products policy since 1996, uninsured rate continues to be high. The 2019 NHMS also reported that 50.1% of the Malaysian population did not have any form of financial protection for healthcare, apart from the subsidised treatment by the government; and 36% of the surveyed population stated that health insurance was not a necessity while 43% stated that they could not afford to buy healthcare insurance.[8]

Low health insurance coverage of cancer patients can lead to upsurge in self-medication, delay in seeking treatment as well as increase in cases of not seeking treatment despite reporting being sick. Health insurance coverage disruptions are common and adversely associated with receipt of cancer care and survival. Lack of health insurance coverage is one of the strongest predictors of poor cancer outcomes in the USA.[18] The uninsured are less likely to receive evidence-based care throughout the cancer control continuum, including prevention and screening, diagnosis, treatment (ie, surgery, radiation therapy and systemic therapies) and symptom management, survivorship and end-of-life care than their counterparts with health insurance coverage. The uninsured are also more likely to have later stage of disease at diagnosis and poorer survival.[19]

As mentioned earlier, PHI policies in Malaysia can be attained on voluntary basis either by individual purchase or through employer-sponsored scheme. The percentage of ownership in the individual purchase health insurance is slightly higher compared to the employer-sponsored insurance. This is also reflected in 2015, where 23.7% had individual purchase and 15% was covered by employer-based health insurance.[20] In the Nordic countries, the market is

Table IV: Logistic regression of the study population (n = 630)

	Simple Logistic Regression			Multiple Logistic Regression		
	cOR	95% CI	*p*	aOR	95% CI	*p*
Age						
18–40	3.06	1.84-5.07	< 0.001	3.01	1.67-5.41	< 0.001*
41–60	2.27	1.54-3.35	< 0.001	2.22	1.41-3.49	0.001*
>60			Reference			
Household income						
B40			Reference			
M40	3.50	2.43-5.04	< 0.001	2.90	1.92-4.39	< 0.001*
T20	6.00	2.93-12.31	< 0.001	3.86	1.68-8.91	0.002*
Home distance from hospital						
Within KV (near)	1.74	1.24-2.46	0.002	1.68	1.10-2.55	0.016*
Outside KV (far)			Reference			
Household size						
1–2 (small)			Reference			
3-6 (medium)	2.72	1.72-4.31	< 0.001	2.20	1.30-3.72	0.003*
> 6 (large)	2.53	1.31-4.89	< 0.001	1.92	0.89-4.14	0.096
Head of household gender						
Male			Reference			
Female	1.40	0.87-2.24	0.165	1.79	1.01-3.16	0.045*
Current cancer treatment						
Follow-up/ Symptomatic	4.19	1.56-11.26	0.005	5.56	1.73-17.89	0.004*
Chemotherapy	3.70	1.40-9.81	0.009	4.40	1.40-13.82	0.011*
Radiotherapy	4.16	1.52-11.41	0.006	6.82	2.07-22.47	0.002*
Chemo-radiotherapy			Reference			
Treatment location						
Inpatient			Reference			
Outpatient	2.47	1.66-3.68	< 0.001	1.97	1.21-3.19	0.006*
Prior treatment in private healthcare facilities						
Yes	5.82	3.39-9.99	< 0.001	4.81	2.57-9.00	< 0.001*
No			Reference			
Financial coping mechanism						
Yes			Reference			
No	2.98	2.13-4.16	< 0.001	2.53	1.72-3.73	< 0.001*

*Significant results.
cOR = crude odds ratio.
aOR = adjusted odds ratio.

dominated by insurance through an employer: in Norway collective/group policies constitute around 90%, in Sweden 72% of insurance policies were paid by the employer, and in Denmark 75% was part of an employment contract. However, in Finland, only 16% of the insured adults had employer-purchased insurance and as many as 75% had self-purchased insurance.[21]

The average monthly premium amount paid in this study was RM263.28 which is comparable with another study in Malaysia on 1000 respondents aged 20–60 whereby the findings showed majority of the respondents paid RM200 for their monthly PHI premium.[22] This amount is fairly affordable considering the adverse selection practice which is common in PHI whereby cheaper plans are designed for young and healthy individuals, and more expensive plans for sick and high risks patients which sometimes can be up to the point of not being affordable. Since public health insurance is not yet implemented in Malaysia, we cannot compare the public and PHI premium in this country; however, this amount was much higher compared to the monthly public health insurance premium of IDR 25,500 to IDR80,000 (RM7.72 to RM24.24) in Indonesia.[23]

Majority of the respondents with PHI was covered for both inpatient and outpatient treatments, which is different from findings from other studies which reported PHI mostly covers hospital inpatient treatments.[24,25] Majority of the respondents with insurance also was covered for certain health services only and not for all types of health services, including surgery. This is in line with why there were respondents with health insurance who were treated in public hospitals and not in private hospitals. As we know, the treatment of cancer may include surgery apart from chemotherapy, radiotherapy or combination treatments. The cost for surgery in the public hospitals is generally much lower than in the private hospitals, thus patients with health insurance which does not cover surgery will tend to have the surgery in public hospitals.

These patients tend to continue their cancer treatments in the public hospitals also due to the convenience for treatment continuation. Besides, the usual waiting time for cancer treatment in public hospitals is within the acceptable one to two months period. However, for cancer patients who have insurance coverage for all types of health services (including surgery) and have their initial surgery and treatment in private hospitals, they might come to public hospitals later to continue their cancer treatments because their insurance benefits might be limited, and they have exhausted their insurance benefits in the private hospitals prior to coming to the public hospitals.

At the moment, Malaysia still does not have a national social health insurance. The type of health insurance available in the country is mainly the PHI. Fuelled by rising incomes as well as increasing urbanisation, healthcare demand and utilisation, the robust private sector in health is not supported by a well-placed health financing system, which consequently led to the ballooning of out-of-pocket (OOP) payments to finance the use of private medical care and an increasing resort to PHI.[26] The Malaysian government has been seeking an alternative scheme to finance health services in a long-drawn out process lasting more than 30 years. In 2002, the government announced the establishment of a health insurance scheme called the National Health Financing Fund to coordinate and provide a more systematic, accessible and equitable health financing system for the Malaysian public. However, the implementation of this scheme was not started due to various limitations and challenges. Thus private funding for health services is still necessary, even in the public hospitals, and that larger companies would be expected to provide health insurance for their employees.[27]

In countries with large publicly funded health systems, PHI fortifies the system by serving a secondary role of supplementing, complementing or duplicating public health services. Through these roles, PHI also allows greater access to private health care that offers preferential choice for timely care, provider, care options and waiting time, which may contribute towards health and well-being. Overall, the role of private insurance varies depending on the economic, social and institutional settings in a country or region. PHI schemes can be valuable tools to complement existing health-financing options only if they are carefully managed and adapted to local needs and preferences.

Although the health insurance is mandatory in many developed countries, the developing countries is yet to impose regulations on the purchase of health insurance. The PHI sector in Malaysia is relatively new but is growing. The main source of health financing in Malaysian public sector is the national taxation, while in the private sector, the main source is OOP.[28] From nearly 60% of Malaysians who seek private primary care, only 18.8% of adult Malaysians are protected with insurance, while the other 73.2% use out-of-pocket (OOP).[29] In Malaysia, there are many PHI providers from local and multinational sectors, but they are not able to capture the full market. The success of this industry and its players depends on the awareness levels of consumers.

The socio-demographic and socio-economic factors can influence a household's decision to purchase a PHI policy. In our study, we found that health insurance usage was significantly higher in male respondents. This is in line with studies that reported males are more prone to have health insurance compared to females.[30,31] This is probably due to the greater involvement of men in the paid labour force and their higher earnings. However, this finding is different from other studies, which show females have more propensities to enroll and renew their health insurance policy compared with males.[32,33] The increased participation of females in the NHIS policy is mostly linked to their motherly role and vulnerability to healthcare.

Among the major ethnic groups in Malaysia, Malay, other Bumiputera and other ethnic groups had higher likelihood of being uninsured, compared with the Chinese and Indians. Abu Bakar et al. (2012) found that race–religion influences individual health insurance demand in Malaysia.[34] Fadlallah et. al (2018) also reported minority ethnicity has positive influence towards the uptake of health insurance in Malaysia.[32] Balqis-Ali et al. (2021) stated the likelihood of being uninsured was higher among Malay/other Bumiputra ethnicities.[25] Joshi and Lim (2010) reported that the Chinese ethnicity was more likely to possess health insurance compared to the other ethnicities.[35] A possible explanation was the income gap between ethnicities in Malaysia. In 2020, the Chinese recorded a median income of RM7391 while the Indians and Malays/Bumiputeras recorded median incomes of RM5981 and RM5420, respectively.[36]

In our study, those aged 18 to 40 were three times, and those aged 41 to 60 were two times more likely to have health insurance, a finding observed in studies that reported the likelihood of being insured increases with younger age.[29,31,37,38] Kefeli and Jones (2012) also stated that both males and females in the age range from 21 to 46 are the most prevalent group to have health insurance.[12] Lower insurance coverage among older age group may be related to the relative young market of PHI in Malaysia, higher premium and risk stratification for older individuals. This inadvertently leaves the older with less choices, limiting them to public health care if they are unable to afford private services. This is different from studies that showed older age positively influences the health insurance purchase.[39-41]

Our study concluded that income was an important predictor of health insurance ownership. The middle-income (M40) group and the high-income (T20) group were found to be three times and six times more likely to have health insurance compared to the lower income (B40) group. In previous studies, the ability of households to enroll and renew their health insurance policy has been linked with the higher income groups compared with those in poor socio-economic standings.[12,40-44] The poor were found to be less likely to purchase a health insurance because they might not be able to pay the required premiums of the health insurance. The insurance premiums can vary greatly depending on the patient's age and disease including the extent and duration of the insurance coverage. With higher PHI premiums, lower income group is less willing and able to pay premiums. This may be explained through the "loss aversion" theory whereby purchasing an additional and non-mandatory item such as a PHI is perceived as a greater monetary loss than the benefit it may offer.[45]

Across different settings, the increase in the education level of households increases the odds of owning a health insurance policy. Our study concluded that there is a significant association between having a health insurance and tertiary education. It has been reported previously that individuals educated at higher level, preferably tertiary, have higher odds of purchasing a health insurance policy.[33,41,46,47] Level of education is directly related to the capacity to accumulate and understand health-related information in making decision to purchase health insurance. Lower level of education may restrict understanding or overwhelm an

individual, and this could lead to "omission bias" whereby one prefers status quo than making a hard decision. Lower education is also directly related to income, affecting the ability to purchase insurance.

Status of employment is an important determinant in the purchase of health insurance. As expected, the employed respondents have a higher probability of purchasing PHI, whereas the unemployed and retired respondents were less likely to buy PHI. Type of occupations was another major demand influencing factor, whereby households engaged in formal occupations that had a constant flow of income were more likely to have health insurance. Previous studies found that ownership of health insurance covers was positively correlated with employment, particularly by formal employment.[32,40,41,48]

Our study recorded higher health insurance usage in private sector employment, which corresponds with Kefeli and Jones (2012) study which shows taking up of PHI is higher among private sector workers.[12] This may be attributed to the comparatively higher socio-economic status and the fixed salary of private sector workers which encourage those households to buy health insurance, whereas the public sector workers don't really need a PHI as they can rely on their government Guarantee Letter (GL) health benefits.

Distance between households and the health centre played a significant role in the decision to enroll in PHI in previous studies. Our study found that respondents who live near the public hospitals have higher insurance uptake and two times likelihood to have health insurance compared to respondents who live far from the hospitals. This can be explained by the aggregation of many public and private hospitals along with many health insurance provider companies in Klang Valley, whereby the patients have easier access to purchase health insurance if they stay within Klang Valley. This finding is supported by Muhlis (2022) study which shows low enrolment in health insurance is associated with insufficient healthcare accessibility and services availability,[49] and Sanhueza and Ruiz-Tagle[30] study which concluded that the probability of an individual and his dependents having a private health plan increases with nearby private providers.

Household size and composition of the household can affect insurance status. In our study, medium household size and female head of households were more likely to be insured. The responsible person to head a family influences their ability to own a health insurance policy. Thus incidentally, households headed by a female were shown to have increased odds of having health insurance. The employment and socio-economic status of these household heads influences their economic ability to purchase a health insurance policy.

The household size has been demonstrated as one of the predictors of health insurance ownership whereby medium household size has been shown to increase the likelihood of having health insurance by about three times more than the small household size. This is supported by Oriakhi and Onemolease[50] study, which reported higher insurance uptake with larger households. This may be as a result of the high financial burden faced by larger households when seeking health care services for individual household members, thus the reason they need to have a health insurance that can cater for the whole household. However, this finding was not consistent with other studies which reported higher insurance uptake in small households.[37,44,51]

The findings from this study identify particular groups of people who were more inclined towards joining a health insurance scheme. Other significant results in the bivariate analysis include receiving combination chemo-radiotherapy treatment, inpatient treatment location, without prior treatment in private healthcare facilities and with financial coping mechanism. These findings however were not reflected in the predictive factor analysis, whereby the logistic regression results were significant for other factors, for example follow-up/symptomatic treatment with five times the odds, chemotherapy treatment with four times the odds, radiotherapy treatment with six times the odds, outpatient treatment location has almost two times the odds, prior treatment in private healthcare facilities has four times the odds and without financial coping mechanism also has two times the odds of having health insurance compared to each reference factors. Further studies need to be carried out among the cancer patients to understand these factors and other factors that attract people to purchase health insurance. At the same time, the behaviour of those who did not join also needs to be studied carefully to identify factors that may deter potential clients from joining any insurance schemes.

LIMITATION OF THE STUDY

The cross-sectional nature of this study did not allow temporal effect analysis on certain variables such as chronic illnesses. Although the factors included in the survey were extensive, it did not cover factors specifically associated with health insurance coverage such as knowledge on health insurance, size effect of insurance premiums, self-assessment of health, risk attitude of members, trust on provider organisation and availability of alternate insurance or other health service options and exemption from payment within universal health coverage. Moreover, this study did not explore the effect of PHI on health care utilisation and impact towards the Malaysian health system landscape, perhaps areas for future study.

CONCLUSION

PHI has been identified as an intermediate step before initiating a social health insurance scheme that will allow the country to build its capacity to manage publicly funded large scale health insurance schemes. However, it is not a silver bullet in increasing efficiency of health financing mechanisms and ensuring access to quality healthcare for all in a middle-income country like Malaysia. The findings of this study in terms of identifying several factors which can influence PHI usage in public hospital settings are expected to have significant implications in terms of designing demand-driven and context-adapted schemes that have greater potential to attract a larger client pool, ensure effective risk pooling and eventually expedite the achievement of universal health coverage, especially for high costing disease like cancer.

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Trust in physician among patients with type 2 diabetes mellitus in Luyang Health Clinic, Sabah and its association with treatment adherence and glycaemic control

Flecia Kundayis, MMed (Fam Med)[1], Mohd Fairuz Ali, MMed (Fam Med)[2]

[1]Klinik Kesihatan Lohan, Ranau, Sabah, Malaysia, [2]Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: A patient's trust in their physician is associated with their self-reported health outcome. However, the relationship between trust in physician with therapeutic and health outcome has not been adequately explored. Therefore, this study aims to assess the level of trust in physician among type 2 diabetes mellitus patients and its association with treatment adherence and glycaemic control.

Materials and Methods: A cross-sectional study was conducted in Luyang Health Clinic from 1st June 2020 to 3rd September 2020. A self-interviewed questionnaire comprises of three sections; sociodemographic, Wake Forest Physician Trust Scale (WFS) and Adherence to Refills and Medications Scale (ARMS) was completed by 281 respondents. Glycaemic control is based on the latest Hba1c profile of the respondents. Descriptive and non-parametric bivariate analysis were performed using IBM SPSS version 26.

Results: The median (IQR) level of trust in physician was 43(8) out of a possible score range of 10 to 50. Trust in physician was correlated with treatment adherence (r=−0.12, *p*=0.048). There was no significant association between trust in physician with sociodemographic factors, which include age (*p*=0.33), gender (*p*=0.46), ethnicity (*p*=0.70), education level (*p*=0.50), and household income (*p*=0.37). Similarly, there was no significant association between the level of trust in physician with glycaemic control (*p*=0.709).

Conclusion: In conclusion, trust in physician was associated with treatment adherence but not with glycaemic control. In our local context, the glycaemic control could be due to other factors. Further studies should include a multicentre population to assess other potential factors that could contribute to glycaemic control.

KEYWORDS:
Trust in physician, treatment adherence, glycaemic control

INTRODUCTION

Trust in a physician has been defined as "a reassuring feeling of confidence or reliance in the physician and the physician's intent"[1] or "a patient's optimistic acceptance of a vulnerable situation and the belief that the physician will care for the patient's interests".[2] Patients who trust their physicians are willing to be vulnerable and believe that the physician puts their best interests in managing their patients' health issues. It is, thus, an important component of the doctor-patient relationship. Trust in physician can be classified into two categories; interpersonal trust and organizational trust.[3] Interpersonal trust relates to the trust that is developed over past interactions or experience with a person. On the other hand, organisational trust or social trust is a trust held by the general society towards an organisation, such as a hospital or a clinic.

Various factors may influence trust in a physician. These include patient's characteristics or values, physician's communication skills, continuity of care and healthcare systems. Older patients and white ethnicity in western countries are associated with higher trust in the physician. Greater trust is reported in elderly patients and white ethnicity because they are involved in making decisions about their madical care and given sufficient time during their consultations.[4,5] Patients' education also may influence trust in physician. Higher education level group patients utilise more healthcare services and interact more with healthcare system.[6] Factors such as, better physician's communication skills and continuity of care also result in higher trust in physicians.[7] Good communication by providing adequate medical information, explaining diseases, listening to the patients and involving the patient in making decisions will increase physician trust.[5,8,9] Healthcare system management may also impact physician trust by restricting choices, contradicting medical decisions and controlling or restricting communication.[10]

Higher trust in physician is associated with patient's self-reported health outcomes, retention in their disease care, increase treatment adherence and patient satisfaction, thus, rendering its importance.[11,12,13] Conversely, poor trust in healthcare is associated with more medicolegal litigations due to poor communication skills and increased use of alternative treatments due to mistrust in the healthcare system.[14] This situation may adversely affect the physicians due to fear of litigation and practice of defensive medicine.[15] Furthermore, the lack of physician trust will lead to poor participation in preventive care programmes.[16]

This article was accepted: 10 May 2023
Corresponding Author: Flecia Kundayis
Email: fleciakundayis@gmail.com

In Malaysia, diabetes mellitus is a major public health concern, and the prevalence of type 2 diabetes mellitus (T2DM) has escalated to 20.8% in adults above the age of 30, affecting 2.8 million individuals.[17] Unfortunately, glycaemic control among Malaysians with T2DM is poor. The National Health and Morbidity Survey (NHMS) 2019, reported that the established diagnosis of T2DM in 2019 was 9.4%, compared to 8.3% in 2015. Furthermore, the diabetes clinical audit done among T2DM patients in 2019 reported only 32.4% of people with T2DM achieved an Hba1c target < 7%, slight improvement from 2013 which was 20.4%.[18] Poor glycaemic control results in increased microvascular and macrovascular complications, as well as premature and preventable mortality.

The study on patient's trust towards primary care provider and its association with diabetes outcome and treatment adherence are limited. Most past studies only focused on assessing the patient's trust level in the physician, while few studies assessed the relationship between trust in the physician and health outcomes.[3,19,20] Patients' trust in physician will reinforce the clinical relationship, directly increasing treatment adherence and improved health outcomes. Some studies were conducted to look at the level of trust in physician among diabetic patients and its relationship with health outcome. Studies done in Taiwan showed that trust in the physician among diabetic patient was associated with the better treatment adherence and diabetes outcomes.[12,21] Trust has contributed to improved patient's health outcomes in term of glycaemic control, quality of life and diabetes self-care.

Similarly, studies assessing the relationship between trust in the physician with therapeutic adherence and health outcome in the local setting are scarce. A local study in 2008, conducted among patients with diabetes in an urban health clinic in West Malaysia, reported that most patients had moderate trust in their physician.[22] In this previous local study, trust in physician was associated with the increase patient satisfaction but not with the glycaemic control. However, the study did not investigate the association of trust in the physician with treatment adherence. In addition, the local study was conducted in West Malaysia on the level of trust in physician was conducted over 10 years ago. The limited local studies on trust in physician are also reported in Sabah. Sabah is a state in East Malaysia with a diverse ethnic distribution of largely indigenous races. To date, no studies are available to measure the current level of trust in physician among Malaysian primary care patients in East Malaysia. This current study assesses level of trust in physician and other potential factors such as cultural difference or different patterns in their trust in the physician which may contributing to treatment adherence and glycaemic control. Therefore, the present study determines the level of trust in physician among patients with T2DM in Luyang Health Clinic, Sabah and its association with treatment adherence and glycaemic control.

MATERIALS AND METHODS

Study Design

This study is a cross-sectional study conducted among adult T2DM patients in Luyang Health Clinic, Sabah. Luyang Health Clinic is an urban primary care clinic located in the Kota Kinabalu district with about 4,896 diabetic patients under its care. Data were collected from 1st June 2020 to 3rd September 2020. The inclusion criteria were patients diagnosed with T2DM for more than a year, taking at least one antidiabetic drug, able to read or understand English or Malay language, and is 18 years of age. Those who refuse to give consent, who are critically ill or in an unstable condition, have a significant cognitive impairment such as intellectual disability and dementia, have a self-reported formal diagnosis of mental illness, and have severe hearing or visually impaired were excluded from being recruited. The sample size for this study was calculated using single mean formula based on the effects of trust in physician on adherence and diabetes outcomes by Lee et al.[12] The minimum sample size required was 281 based on the desired confidence interval of 95%, with a standard deviation of 11.48, precision (d) of 1.5 and an expected non-response rate of 20%. Using the systematic sampling approach, every sixth person who registered at the counter was approached for recruitment. The first respondent for each day was selected according to a random starting point and subsequent sampling selection according to the interval. If the patient declined to participate, the subsequent sixth patient would be approached. All the respondents were briefed about this study and had given their written consent.

Study Instrument

The questionnaire contained four sections: (1) sociodemographic questions, (2) Wake Forest Physician Trust Scale (WFS),[23] (3) Adherence to Refills and Medications Scale (ARMS),[24] and (4) latest Hba1c profile of respondents. WFS and ARMS questionnaires were both validated. WFS was a 10-item questionnaire developed to measure trust in the physician. It showed high internal consistency with a Cronbach's alpha of 0.93. The responses were based on the five-point Likert scale, where 1 reflects "strongly disagree" and 5 reflects "strongly agree". Items 2, 3, and 8 were reverse coded. The score was the total score for all questions answered in a range of 10 to 50. A higher score indicates higher trust.[23]

Meanwhile, ARMS was a 12-item questionnaire developed to measure treatment adherence and designed specifically for populations with low level of health literacy, making it suitable for the local population. ARMS had high internal consistency with Cronbach's alpha of 0.81. The responses were based on the five-point Likert scale, where 1 reflects "none" and 4 reflects "all". Item 12 is reverse coded. The score was the total score for all questions answered in a range of 12 to 48. Lower scores indicated higher adherence.[24]

The HbA1c profile of respondents was based on the latest HbA1c result. HbA1c under 7% is considered appropriate for most adult T2DM individuals based on the Malaysian Clinical Practice Guideline Management of T2DM recommendation. Both WFS and ARMS were translated into Malay using the standard forward and backward translation process. A pre-test was conducted among five patients with diabetes mellitus for face validation to check the understanding of the questionnaires and appropriateness of wording. Subsequently, a pilot testing was then performed on 30 respondents in the Luyang Health Clinic. Cronbach's

Table I: Sociodemographic profile of the respondents (n = 281)

FaVariables	N	%	Median (IQR)
Age (years)			65 (13)
≥ 60 years of age	196	69.8%	
<60 years of age	85	30.2%	
Gender			
Female	152	54.1%	
Male	129	45.9%	
Ethnicity			
Chinese	173	61.9%	
Bumiputra Sabah	82	29.2%	
India	7	2.5%	
Malay	5	1.8%	
Others	13	4.6%	
Education			
No education	57	20.3%	
Primary education	86	30.6%	
Secondary education	87	31.0%	
Pre-university	11	3.9%	
Tertiary education	40	14.2%	
Household income			
Low	263	93.6%	
Middle	12	4.3%	
High	6	2.1%	
HbA1c level			6.9 (2.1)
Good control (<7.0)	147	52.3%	
Poor control (≥7.0)	134	47.7%	

IQR = Interquartile range

Table II: Level of trust in physician among type 2 diabetes mellitus patients (n = 281)

Variable	Median (IQR)	Min, Max value
Level of physician trust in physician among T2DM patients	43 (8)	34,50

IQR = Interquartile range

Table III: Association between sociodemographic factors (age, gender, ethnicity, education level and household income) with level of trust in physician among type 2 diabetes mellitus patients (n = 281)

Variables	n	%	Trust in physician level Median (IQR)	*p* value
Age (years) [a]				
≥ 60 years of age	196	69.8%	43.0 (8)	0.33
<60 years of age	85	30.2%	43.0 (7)	
Gender[a]				
Female	152	54.1%	43.0 (8)	0.46
Male	129	45.9%	42.0 (8)	
Ethnicity[b]				
Chinese	173	61.6%	43.0 (7)	0.70
Bumiputra Sabah	82	29.2%	41.0 (5)	
India	7	2.5%	41.0 (8)	
Malay	5	1.8%	42.5 (8)	
Others	13	4.6%	41.0 (9)	
Education level[b]				
No education	57	20.3%	44.0(9)	0.50
Primary education	86	30.6%	42.0(7)	
Secondary education	87	31.0%	44.0(7)	
Pre-university				
Tertiary education				
Household income[b]				
Low	263	93.6%	43.0(7)	0.37
Middle	12	4.3%	47.0(9)	
High	6	2.1%	43.0(13)	

[a]Mann-Whitney U test
[b]Kruskal-Wallis test
*significant $p<0.05$

Table IV: Level of treatment adherence among type 2 diabetes mellitus patients (n = 281)

Variable	Median (IQR)	Min, Max value
Level of treatment adherence among T2DM	13 (2)	12,21

IQR = Interquartile range

Table V: Correlation between level of trust in physician among type 2 diabetes mellitus patients with treatment adherence (N=281)

	Treatment adherence	
Variable	r value	*p* value
Level of trust in physician among T2DM patientsa	-0.12	0.048*

[a]Spearman correlation
*significant $p < 0.05$

Table VI: Association between level of trust in physician among type 2 diabetes mellitus patients with glycaemic (n = 281)

	Glycaemic control			
Variable	Good control (HbA1c < 7.0%)	Poor control (HbA1c ≥7.0%)	U value	*p* value
Level of trust in physician among T2DM			9597	0.709
Median (IQR)	43 (7)	43 (8)		
Mean rank	142.71	139.12		

[a]Mann-Whitney U test
*significant $p < 0.05$

alpha value for 10 items of WFS was 0.78, and 12 items of ARMS was 0.73, indicating good reliability.

Data Analysis

Data were analysed using IBM SPSS Statistics version 26 and presented in frequencies, percentages and medians (IQR) where appropriate. Normality testing was done for numerical variables. Non-parametric bivariate analysis was performed in view the skewed distribution for numerical variables. The Mann-Whitney and Kruskal-Wallis tests were used to assess the association between sociodemographic factors and level of trust in physician. Spearman's correlation was used to assess the correlation between trust in physician and treatment adherence. The Mann-Whitney test was used to assess the association between trust in physician and glycaemic control.

RESULTS

A total of 330 respondents were approached for this study, and 281 agreed and completed the questionnaires, giving a response rate of 85.1%. Most of the respondents were over 60 years of age (69.8%), female (54.1%), Chinese (61.9%), had an education up to secondary level (31.0%) and mostly from the lower income group (93.6%). About half had good glycaemic control with HbA1c <7.0 (52.3%) (Table I).

Level of Trust in Physician

Out of 281 respondents, the median level of trust in physician was 43 (IQR 8). The lowest score was 34, and the highest was 50 out of a possible score range of 10 to 50 (Table II).

Association Between Sociodemographic Factors with Level of Trust in Physician

The level of trust was not significantly associated with any of the sociodemographic factors, which include age (p=0.33), gender (p=0.46), ethnicity (p=0.70), education level (p=0.50), and household income (p=0.37) (Table III).

Level of Treatment Adherence

From 281 respondents, the median level of treatment adherence was 13 (IQR 2). The lowest score was 12, and the highest was 21 out of a possible range of 12 to 48 (Table IV).

Correlation Between Level of Trust in Physician with Treatment Adherence

Spearman's correlation was used to determine the correlation between the level of trust in physician among T2DM and treatment adherence. Table V and Figure 1 showed a significantly weak negative correlation between level trust in physician with treatment adherence among the respondents (r=-0.12, p=0.048). Lower scores indicate better adherence; hence, better trust in physician was correlated with better treatment adherence.

Association Between Level of Trust in Physician and Glycaemic Control

The Mann-Whitney U test was used to determine the association between the level of trust in physician among T2DM and glycaemic control. Table VI shows no significant association between the level of trust in physician with glycaemic control among the respondents (p=0.709).

DISCUSSION

Trust in physician is scarcely studied, especially in the setting of developing countries. Several data on this aspect were confined to the western population. This study is known to be the first conducted in Sabah, aimed at assessing the level of trust in physician among T2DM in the urban population of the Luyang area, a town comprising of multiple ethnicities that also includes the local natives unique to Sabah. Overall, the respondents have relatively higher trust towards their physician, with a total median of 43 (IQR 8) out of a possible score range of 10 to 50.

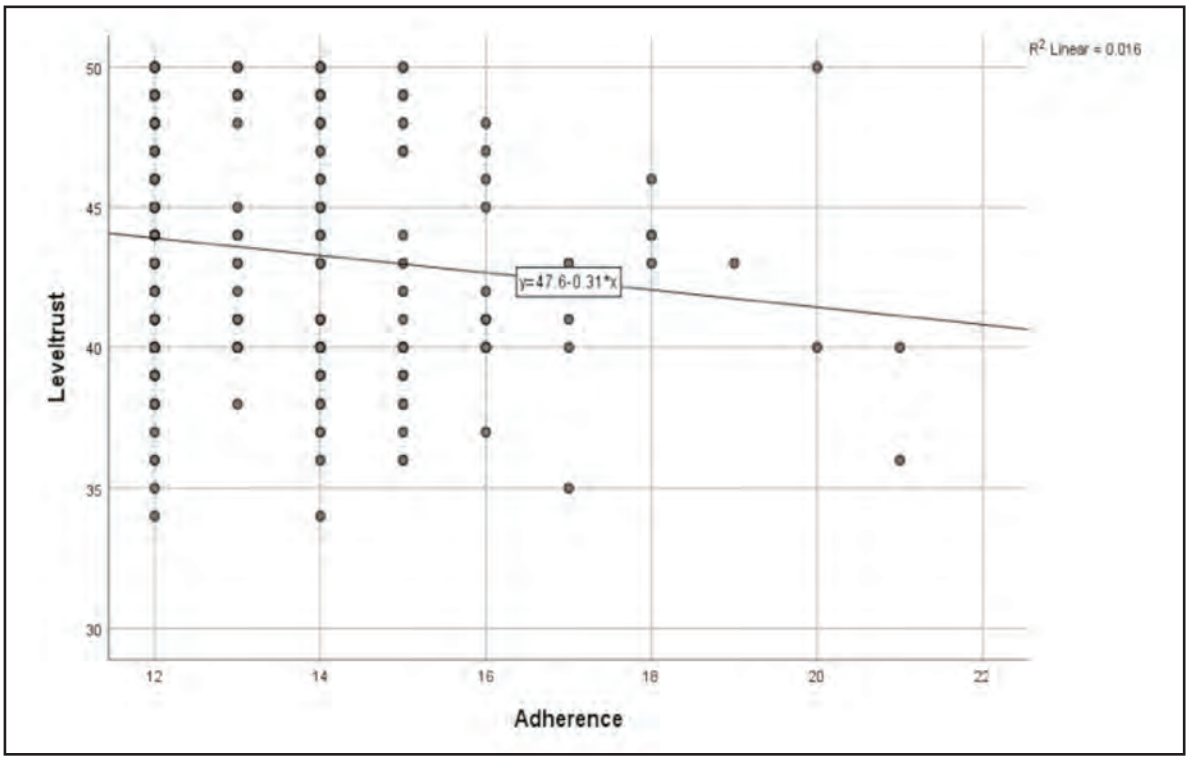

Fig. 1: Correlation between level of trust in physician among type 2 diabetes mellitus with treatment adherence

The median trust of this study is higher than the previous study.[23] A possible reason could be that most of the patients were elderly, and they have been following up in the Luyang clinic for many years. The patients had a long relationship with their regular doctors and were seen by a regular doctor each time follow up. Currently, Luyang clinic has been practising Family Doctor Concept (FDC). In this concept, each patient will be assigned to a doctor who will take care of their illness. Being seen by the same healthcare provider at every follow up will create a good doctor-patient relationship, which will enhance the continuity of care, and patient's compliance towards their treatment and management provided. The previous study has shown that the greater continuity of care between patients and healthcare providers, the higher their trust in their physician.[7]

The median (IQR) age of respondents was 65.[13] Approximately 69.8% of the respondents were ≥ 60 years of age and above. There was no significant association was noted between respondents' age and trust level in physician in this study. This finding contradicts with a study conducted in the United States of America (USA) that showed a positive association between age and physician trust, whereby elderly was associated with higher trust in physician.[5] The previous study was inconsistent with this study due to the variation of comorbidities and health status among these patients, impacting their trust in the physician.[25] Different ages have different comorbidities and health statuses, affecting their frequency of visits to the clinic. In previous study, elderly group given more time to shared care their disease. In this current study, most respondents receiving care at the clinic were mainly the elderly. The group utilises more healthcare services and interacts more with healthcare systems, resulting in the dilutional effect of age on physician trust. Similarly, the younger age group of this study also maintained a high level of trust in physician. One of the reasons could be that the patients in Luyang health clinic were given enough time for consultation to share their disease care and management plan of their disease since the implementation of the FDC at the clinic. FDC implementation had built up a good relationship and rapport between patient and physician as they were attended by the same doctor each time their follow-up. Thus, this has impacted their trust in the physician to be no difference regardless of their age.

Although the proportion of female respondents (54.1%) was higher than male respondents (45.9%) in this study, no statistically significant difference was observed in the trust in physician level among respondents according to gender. This is consistent with a previous study showing that gender was not associated with trust in physician.[26]

The majority of the respondents were Chinese (61.6%), followed by Bumiputra Sabah (29.2%), and other races, mainly Filipinos (4.6%). Despite the different races, their culture and attitude towards healthcare providers were generally similar, as no statistically significant difference was noted between trust in physician with ethnicity in the study population. These findings were consistent with other studies, showing that race was not significantly correlated with patient's trust.[2,3,27] Unlike western populations, minority groups exhibited mistrust towards healthcare providers due to certain reasons.[28] Another study in the USA showed that the white ethnicity patients were significantly associated with a higher level of trust than other ethnicities.[4] These findings were due to racial concordance between patient and physician. In Sabah, the various ethnicities have a good understanding and respect for one another. All ethnic groups

are treated equally in the clinic, hence, the absence of significant trust levels difference.

The majority of the respondents had completed their secondary education (31%). However, only (14.2%) completed their tertiary education, while the other respondents had neither education (20.3%) nor completed their primary education (30.6%). There was no significant association between the education level of the respondents with trust in physician level. This finding was not consistent with a previous study where higher education was associated with higher trust level in physician.[6] Higher education level group patients utilise more healthcare services and interact more with healthcare system. The previous finding was not similar in our society, as most patients in this population will see their doctors when needed and most patients will play assertive roles when encountering care providers regardless of their educational level background.

The majority of the respondents had a low household income (93.6%). No statistically significant difference in the level of trust in physician among respondents was observed according to their household income. This was consistent with a previous study showing that household income was not associated with trust in physician.[6]

A significant association was found between trust in physician with treatment adherence. Better trust in physician was correlated with better treatment adherence. Aspects of trust are essential to a patient's medication compliance. This finding was consistent with a previous study where higher trust in physician will increase patients' likelihood to adhere their medications.[29] In addition, higher trust in physician was also associated with reduced difficulty in adhering to their treatment.[12,30] Training interventions to improve physician competency, communication or provide the patients with more information about their treatment and give them a chance to discuss options might increase the patient's trust in the physician, and indirectly improving their adherence towards medications.[31] When trust in physician higher, patient will likely take their medication as advised by their regular doctor. Thus, it is important to educate physician to improve patient's trust by built up a good relationship and rapport with their patient.

The respondents' median HbA1c was 6.9 (IQR 2.1). Most respondents had good control of diabetes, with HbA1c < 7.0 (52.3%). No significant association was noted between the level of trust in physician with their glycaemic control. It was consistent with a local study done in West Malaysia, which showed no association between trust in physician with glycaemic control.[22] However, this finding was inconsistent with other study done in Taiwan, which showed trust in physician were significantly correlated to patient's diabetes outcome.[12,21] Trust might not be an independent factor influencing glycaemic control in our population because many other factors can influence glycaemic control other than trust in physician alone. Past studies have shown that diabetic control can be influenced by other factors such as length of doctor-patient relationship, the number of visits with the doctor, physician's character and communication.[27] Diabetes outcome were also influenced by the patients' comorbidities, adherence to the diet, and physical activity.[32-34] These factors could have a stronger influence on diabetes outcome than trust in physician, resulting in a lack of association between trust in physician and glycaemic control in this study. More studies are needed to confirm or disprove these potential factors and need to be confirmed in a larger population because the results of this study were only specific to one population.

LIMITATIONS

Although this study was the first local study that looking on trust level in physician among Malaysian primary care patients in East Malaysia and its effect towards health outcome, it had a few limitations. First, this study was a cross-sectional study; hence, the longitudinal dimension relationship between trust and health outcome could not be confirmed. Second, social desirability bias might occur due to the self-interviewed questionnaire. Third, the study population only limited to one centre. This study was conducted in an urban area, and the results might not reflect whole Sabah's population. The respondents were generally similar in terms of age, ethnicity, and socioeconomic status in this study. This similarity might result in identical cultural practise and attitude towards healthcare providers, which may affect their trust towards their physician. Lastly, this study did not collect information on other potential factors that may potentially affect diabetes control, such as doctor-patient relationship, comorbidities, diet, and physical activity. These factors may potentially effect on glycaemic control and should be explored in future studies.

CONCLUSION

This study shows that trust in physicians was relatively high in T2DM patients. In conclusion, trust in physician was significantly correlated with treatment adherence, but it is not associate with glycaemic control. Similarly, no significant association was seen between trust in physician with all the sociodemographic factors (age, ethnicity, gender, education level and household income). Future studies are recommended to explore on the gaps that found in this study, which has been mentioned earlier in the discussion. In this study, the age, ethnicity and socioeconomic status of the respondents were generally similar. This similarity might result in their cultural practise and attitudes towards healthcare providers being generally identical, resulting in similar trust towards physicians. Thus, future research that includes a multi-centre population is recommended to provide a more accurate representation of the Malaysian population. In addition, it would be better to explore other types of trust, such as trust in other medical healthcare workers or healthcare systems.

ACKNOWLEDGEMENT

The author would like to thank all the respondents who voluntarily participated in this study and the Ministry of Health for the permission to conduct this study.

FUNDING AND CONFLICT OF INTEREST

This study was self-funded and there was no conflicts of interest.

ETHICAL APPROVAL

This study was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR-18-3894-45364). Permission to use both the questionnaires have been obtained from the respective authors. Permission to conduct the study at the Luyang Health Clinic, Kota Kinabalu, Sabah, was also obtained from the Sabah State Health Department, Kota Kinabalu District Health Office, and the Family Medicine Specialist (FMS) in charge of the clinic. All respondents who took part in this study had given their written consent.

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ORIGINAL ARTICLE

Mindfulness-based therapy for smoking cessation and mental health: a randomised controlled trial

Hemanath Sinnathamby, MPH[1], Fredie Robinson, PhD[1], Nicholas Pang Tze Ping, MMed(Psychiatry)[1], Lim Eng Kean, MClinPsych[1], Ong Shi Joe, MClinPsych[1], Alyssa Suraya, MClinPsych[1], Joshua Selvaraj, MClinPsych[1], Lau Jia Qi, MClinPsych[1], Lim Yong Xin, MClinPsych[1], BPharm(Hons)[2]

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Malaysia, [2]Sepang District Health Office,Ministry of Health Malaysia

ABSTRACT

Introduction: Effective smoking cessation programmes are essential for assisting smokers in quitting, indirectly lowering mortality and morbidity associated with smoking. Numerous studies have indicated positive outcomes when using mindfulness treatment (MT) to treat psychological or behavioural health issues. Although to date, no study has looked at the effectiveness of online MT for quitting smoking while addressing mental health, particularly among the Asian population. Therefore, this study compares the efficiency of online MT to traditional counselling therapy (CT) in aiding smoking cessation programmes while also addressing mental health.

Materials and Methods: A randomised control study with a two-group, single-blind design and baseline evaluation was selected. Social media sites were used to advertise for participants, who were then admitted after meeting the requirements. Participants who met the eligibility requirements were randomly split into two groups. Each group received a total of three sessions of online therapy (MT or CT), once every two weeks, as well as one phone call per week as reinforcement. At the beginning and end of the intervention, participants completed questionnaires (1st week and 5th week). Generalized Estimating Equation (GEE) statistical analysis was used to analyse all the variables.

Results: The MT group experienced a statistically significant decrease in cigarette consumption (β: -3.50, 95% Wald CI: -4.62, -2.39) compared to the CT group over time. Furthermore, the MT group demonstrated significant improvements in their scores for the AAQ-2, anxiety, stress, depression and mindfulness compared to the CT group.

Conclusion: Online MT is more successful at assisting smokers in lowering their daily cigarette intake and supporting their mental health during the smoking cessation process. Further longitudinal comparisons of the effectiveness of online MT should be undertaken using online platforms in future studies.

KEYWORDS:
Smoking cessation, quit smoking, mental health, mindfulness, stress, psychological inflexibility, experiential avoidance

INTRODUCTION

More than 8 million people are estimated to die each year from the tobacco epidemic, with 1.2 million of those deaths attributed to second-hand smoke and 20% of the world's population being smokers.[1,2] An estimated 80% of tobacco smokers reside in low- and middle-income nations, and the impact there is considerably greater according to the World Health Organization.[3] Additionally, smoking is particularly difficult to stop due to the addictive ingredient it contains as well as the habitual behaviour of smoking.[4] The majority of solutions depend on behavioural therapies that teach patients how to avoid triggers, lessen bad moods, distract attention from cravings, promote good affective states, lessen stress, establish social support systems, or replace smoking with alternative activities.[5] Unfortunately, less than 5% of the smokers who try to stop each year succeed.[6] The low success rate may be due to the constant presence of smoking cues, such as positive and negative triggers, which make avoidance practically impossible.[7,8] Furthermore, there is substantial evidence that seeking is caused by smoking mainly due to the psychophysical qualities of nicotine, which is one of the reasons nicotine addictions itself is one of the reasons a person craves cigarettes.[9]

Individuals who try to quit smoking and attend physicians are always more focused on smoking abstinence but neglect the mental roller-coaster journey the individual is going through during the duration of smoking cessation. Many people claim that smoking tobacco reduces their stress levels, helps them deal with mental health issues like depression or anxiety, and gives them a sense of relaxation or pleasure.[10] It might, occasionally, feel as though we are robbing them of one of their "greatest pleasures" when we talk about quitting smoking.[11] This is because nicotine contains inside cigarettes, stimulates the body to release numerous pleasureful neurotransmitters.[12,13] Hence, when a person quits smoking, the nicotine level starts to deplete in the system, creating mental health issues such as anxiety, stress and depression. Therefore, addressing mental health issues associated together with smoking cessation is crucial to ensure success in the programme.

By focusing on the aforementioned factors, namely addiction and craving, positive and negative triggering factors, and teaching them to take action, mindfulness therapy (MT) may

This article was accepted: 10 May 2023
Corresponding Author: Fredie Robinson
Email: freddie@ums.edu.my

be an effective behavioural treatment to stop smoking. MT has demonstrated great efficacy in psychological disorders involving pain, anxiety and depression.[14] Its primary goal is to sustain and regulate a person's current experience and their sense of acceptance of the sign and symptoms caused by smoking cessation.[15] As a result, rather than experiencing the withdrawal symptoms take control of them, the person will be able to perceive their mental state and acknowledge these changes in their mind and body, which helps them quit smoking and helps in regulating mental health status as well.[16-18]

Reductions in substance usage, such as cocaine, alcohol, marijuana, opiates, amphetamines and cigarettes, were strongly associated with MT.[17,19] However, these experimental plans lacked addressing MT's effectiveness in addressing mental health issues associated with smoking cessation. Therefore, it has been hoped that additional randomised controlled trials will be carried out to examine the effectiveness of MT helps in coping with mental health issues in the journey of smoking cessation. This is especially true in Malaysia, where non-directive counselling strategies are currently used in settings, and studies on mindfulness and quitting smoking in relation to managing mental health issues are lacking. A change in therapeutic practice in Malaysian settings would be made possible by high-quality studies on the effectiveness of MTs conducted in Malaysian populations. Therefore, this study's primary goal was to compare the effectiveness of MT to counselling therapy (CT) through a randomised controlled trial study that was intended to help people quit smoking and aid their mental health.

MATERIALS AND METHODS

This study, a single-blind, randomised control trial, took place between July 2 and September 3, 2022. The study were carried out in Malaysia and before being enrolled in the trial, every participant provided online informed consent.

G-Power software 3.1 were used to estimate sample size.[20] The sample size estimate was based on the references that were available and related to MT in smoking cessation,[21–23] as there hasn't been a study that included MT as a smoking cessation aid in Malaysia. An earlier study conducted in Hong Kong served as the basis for the final pooled effect size, which was 0.475.[24] The final computation tabulated 44 participants with a critical F value of 4.15, a significance level of 0.05 and a power of 0.90. Participants were attracted via social media channels and adverts that promoted and offered behavioural treatments for quitting smoking. Adults aged 18 to 60 were required to meet the following inclusion criteria: they had to be able to understand Malay and English to a some degree, they had to be current residents of Malaysia, and the intensity of smoking should be moderate and severe according to pack year calculation. As for the exclusion criteria, they were as follows: having participated in or been enrolled in any other smoking cessation programme run by a private or public healthcare facility (quit smoking clinics) within the previous three months, using any form of nicotine replacement therapy (including e-cigarettes), currently using any form of psychoactive medication, having a serious or unstable medical or mental condition. Additionally, a study by Magill et al. was used to inspire a few actions that were taken to prevent contamination.[25] One of the steps was for each group to have therapy from a different therapist, which made sure that the therapist does not reveal information about another therapy and that it was monitored through the session recordings. The therapist received training in either mindfulness or counselling, but not in both, depending on the group to which they are assigned. Moreover, every participant was given instructions on how to keep the information they have learned in therapy sessions to themselves; any who fail to abide by this guideline were warranted to be expelled from the programme. Furthermore, concealed from the participants is the type of intervention being taught. Finally, participants who agreed to participate and met the eligibility requirements were randomly assigned to groups A (Mindfulness) and B (Counselling) using computer-generated randomisation software.

The intervention was conducted by licensed clinical psychologists and the counselling therapy is based on the Malaysian Clinical Practice Guidelines Treatment of Tobacco Use Disorder 2016. Meanwhile, MT was based on acceptance and commitment therapy. We employed the "being in the present moment" skills and used breathing and grounding exercises with the clients. Emphasis was put on focusing on the present moment with openness, flexibility, kindness and acceptance of the difficult emotions experienced.

The study began with baseline screening of participants using a series of questionnaires to determine their smoking status, mental status and mindfulness state. Based on this initial data, participants were evaluated for eligibility. The intervention and control groups then underwent three therapy sessions, with a 2- week gap between each session, conducted online using Google Meet. The intervention group received MT, while the control group received CT. The therapists also phoned each participant over the 2-week interval to reinforce the lessons. A series of questionnaires were administered again a week after the third session ended to track the progress towards quitting smoking, and again after 5 weeks. At the end of the study, participants who had stopped smoking tobacco were the main outcome. Using the chi-square test, the abstinence rate was compared between the groups. Meanwhile, the secondary result involved using standardised dual language questionnaires to assess the levels of mindfulness, experiential avoidance, psychological rigidity, depression, stress and anxiety. The number of cigarettes smoked each day was analysed using Generalized Estimating Equation (GEE).

Ethics approval was obtained from the Universiti Malaysia Sabah Ethical Board (Code: JKEtika 2/21 – 9) and registered in the Chinese Clinical Trial Registry (ChiCTR) (ID: ChiCTR2200056204).

RESULTS

A total of 110 people volunteered to participate in the study, but 61 had to be withdrawn due to their ineligibility. The 49 participants who met the eligibility requirements were randomly assigned to one of two groups: MT (Group A = 25) or CT (Group B = 24).

Table I: Categorical baseline data and cigarette smoking abstinence rate at the end of the study result

Variables	Category	Group		N = 49 (%)	Chi²	*p* value
		MT (%)	CT (%)			
Sex	Male	24 (53.3)	21 (46.7)	45 (91.8)	-	0.349**
	Female	1 (25.0)	3 (75.0)	4 (8.2)		
Education level	Degree and above	9 (47.4)	10 (52.6)	19 (38.8)	0.176	0.916*
	Diploma and above	6 (54.5)	5 (45.5)	11 (22.4)		
	SPM	10 (52.6)	9 (47.4)	19 (38.8)		
Medical illness	None	17 (51.5)	16 (48.5)	33 (67.3)	-	1.000**
	Chronic illness (one or more)	8 (50.0)	8 (50.0)	16 (32.7)		
Household income	T20	7 (53.8)	6 (46.2)	13 (26.5)	1.060	0.589*
	M40	11 (57.9)	8 (42.1)	19 (38.8)		
	B40	7 (41.2)	10 (58.8)	17 (34.7)		
Type of cigarettes	Filtered	22 (47.8)	24 (52.2)	46 (93.9)	-	0.235**
	Non-filtered	3 (12.0)	0	3 (6.1)		
Abstinence rate at the end of the study	Quit smoking	4 (66.7)	2 (33.3)	6 (12.2)	-	0.667**
	Still smoking	21 (48.8)	22 (51.2)	43 (87.8)		

*Chi-Square test
** Fisher's Exact test

Table II: Numerical baseline data result

Variables	MT (Mean Rank)	CT (Mean Rank)	MT (Sum Ranks)	CT (Sum Ranks)	Mann-Whitney U	*p* value
Age	23.92	26.12	598.0	627.0	273.0	0.588
No. cigarette	25.94	24.02	648.5	576.5	276.5	0.629
MAAS	24.40	25.63	610.0	615.0	285.0	0.764
AAQ – 2	23.46	26.60	586.5	638.5	261.5	0.440
DASS – Depression	26.02	23.94	650.5	574.5	274.5	0.606
DASS – Anxiety	26.88	23.04	672.0	533.0	253.0	0.340
DASS – Stress	25.04	24.96	626.0	599.0	299.0	0.984
Pack Year	23.76	26.29	594.0	631.0	269.0	0.535

Table III: Association of mindfulness and counselling groups between all variables over time

Variables	Time	Mean		df	Wald Chi²	*p* value
		MT (SD)	CT (SD)			
No. cigarettes smoked	Baseline	16.52 (4.16)	16.04 (4.32)	1	37.78	<0.001
	1st reading	11.72 (3.57)	14.00 (5.23)			
	2nd reading	6.64 (4.46)	13.17 (6.41)			
MAAS	Baseline	60.28 (23.78)	62.88 (20.85)	1	36.47	<0.001
	1st reading	72.56 (12.26)	62.96 (20.78)			
	2nd reading	85.36 (4.70)	63.08 (20.59)			
AAQ-2	Baseline	21.68 (13.71)	24.58 (12.58)	1	10.40	0.001
	1st reading	16.72 (9.28)	23.29 (10.64)			
	2nd reading	11.12 (5.81)	21.42 (9.21)			
DASS- anxiety	Baseline	5.36 (2.81)	4.71 (2.77)	1	33.75	<0.001
	1st reading	4.04 (2.57)	5.38 (2.67)			
	2nd reading	3.52 (2.73)	5.33 (2.78)			
DASS- stress	Baseline	5.24 (3.22)	5.50 (2.52)	1	25.74	<0.001
	1st reading	4.16 (2.64)	12.42 (4.20)			
	2nd reading	3.88 (2.49)	9.50 (5.53)			
DASS - depression	Baseline	5.52 (4.17)	5.08 (3.48)	1	39.68	<0.001
	1st reading	3.92 (3.12)	5.50 (3.55)			
	2nd reading	3.28 (2.82)	5.58 (3.54)			

Table IV: Associated effect of mindfulness therapy and counselling therapy between all the variables over time

Variables (reference = MT)	β	95% Wald Confidence Interval		p-value
		Lower	Upper	
No. cigarettes smoked	-3.50	-4.62	-2.39	<0.001
MAAS	12.44	8.40	16.47	<0.001
AAQ-2	-3.70	-5.94	-1.45	0.001
DASS- anxiety	-1.23	-1.65	-0.82	<0.001
DASS- stress	-2.68	-3.72	-1.65	<0.001
DASS – depression	-1.37	-1.79	-0.94	<0.001

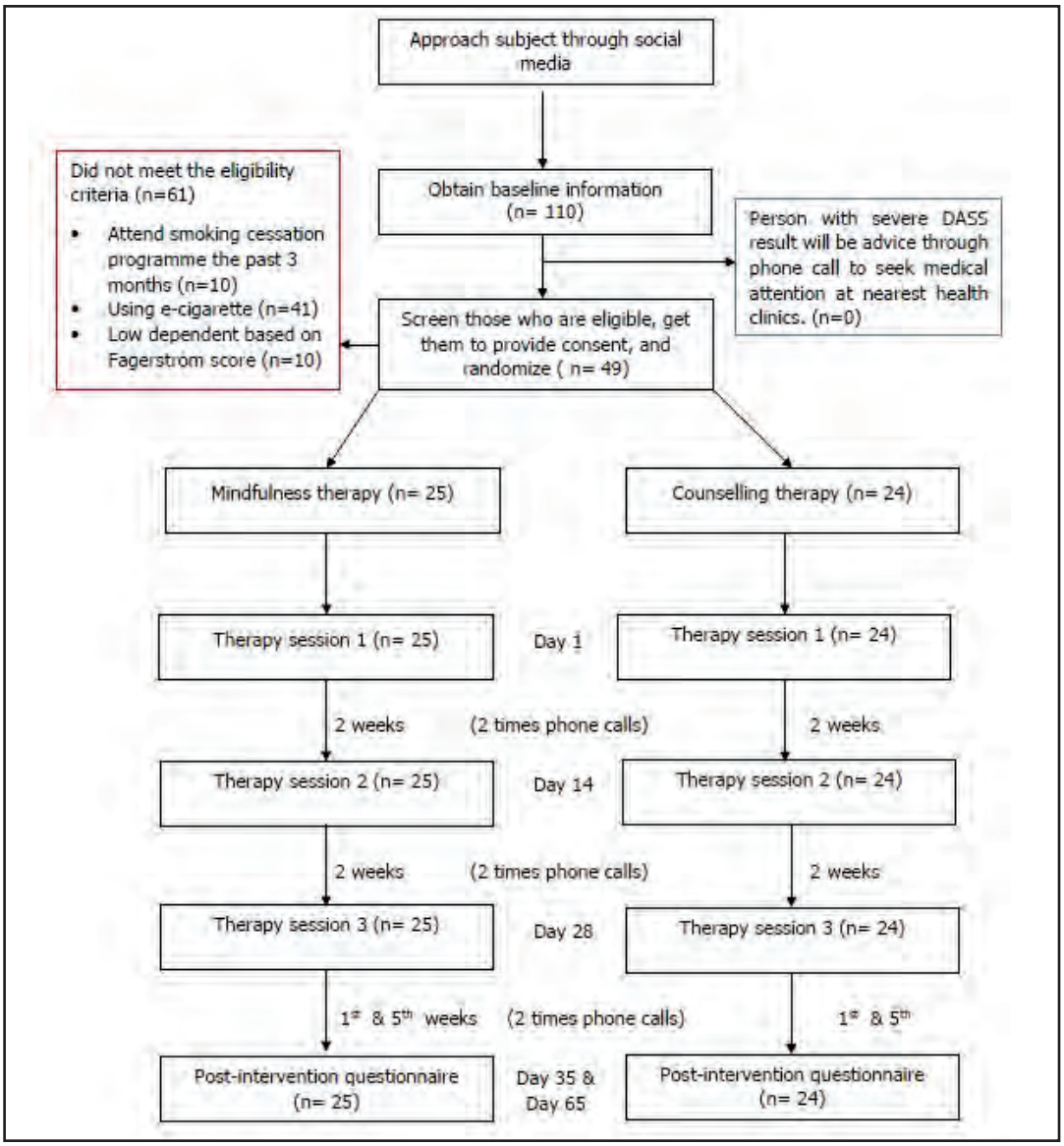

Fig. 1: Study protocol

Both the groups had similar characteristics in terms of sex, age, education level, history of chronic illnesses, family income, cigarette smoking habits, pack year, number of cigarettes smoked per day, Mindful, Attention, Awareness Scale (MAAS), The Acceptance and Action Questionnaire (AAQ-2) score, and Depression, Anxiety and Stress Scale (DASS). All the sociodemographic (sex, education level, chronic medical illness history, household income, type of cigarettes smoked, and pack year) variables tested did not differ significantly differ between the participants of both groups (Tables I and II). Male participants were higher than female participants (8.2%) with a margin of 91.8%. In addition, both the groups smoked almost about the same number of cigarettes per day according to analysis show in Table II.

The MT group had an abstinence rate of 16% (n=4) at the end of the study, while the CT group had an abstinence rate of 8.3% (n=2); however, the p-value was 0.667. The number of cigarettes smoked per day was considerably lower in the MT group at the end of the study compared to the CT group, with a significant p-value of <0.001. Furthermore, there was a significant difference between the MT and the CT group on the MAAS test, with a significant *p* value of < 0.001. At the end of the trial, AAQ-2 score in the MT group (11.12 ± 5.81) improved more than the CT group (21.42 ± 9.21), with a *p* value of 0.001. Even though both the groups' stress levels were normal, we were still able to observe that the CT group experienced higher levels of stress during the smoking cessation phase than the MT group, with a significant p-value of < 0.001. Similar findings seen in the DASS score of anxiety and depression whereby the mental status of the participants in the MT group were under controlled compared to the participants in the CT group.

The regression analysis results, presented in Table IV, demonstrated that the MT group experienced a significant decrease in cigarette consumption of 3.5 cigarettes per day (95% Wald CI: -4.62, -2.39) compared to the CT group over time. This reduction is statistically significant, as indicated by a p-value of <0.001. The analysis also indicates that the MT group showed significant improvements in their AAQ-2 score,

anxiety, stress and depression, with an average reduction of 3.70 (95% Wald CI of –5.94 to -1.45, *p* value 0.001), 1.23 (95% Wald CI of -1.65 to -0.82, *p* value < 0.001), 2.68 (95% Wald CI of -3.72 to -1.65, *p* value < 0.001), and 1.37 (95% Wald CI of -1.79 to – 0.94, *p* value < 0.001), respectively, compared to the CT group over time, after adjusting for time period and intervention groups. Moreover, the MT group demonstrated a significant average increase of 12.44 (95% Wald CI of 8.40 to 16.47, *p* value < 0.001) in their MAAS score compared to the CT group. These findings suggest that the MT intervention can effectively reduce cigarette consumption while preserving mental health status.

DISCUSSION

MT is a systematic programme that teaches individuals how to control their attention and self-control while maintaining an attitude of acceptance and openness to external and internal stimuli.[26,27] Given that the main clinical symptoms of any addiction are intoxication, bingeing, craving and withdrawal. MT may be beneficial as a coping mechanism because it helps people become aware of their intoxication as well as control their bingeing, craving, and withdrawal, which together act as a bulwark against negative emotions and stress reactivity.[27]

This is the first clinical trial in Malaysia to test online MT to aid in smoking cessation. In clinical practice, psychologists may use MT as an integrated part of a smoking cessation programme. However, this is the first time looking at outcomes of an independent mindfulness intervention in an experimental study design. Even though the abstinence rate difference between the MT group and the CT group was statistically insignificant, MT nonetheless showed numerically better abstinence results. The large decrease in daily cigarette consumption is a crucial step in the process of quitting smoking. Researchs suggest that those who smoke fewer cigarettes per day are more likely to succeed in quitting.[28,29] Furthermore, cutting back on cigarette consumption is strongly linked to lower death rates, lower rates of lung cancer and lower rates of respiratory illnesses.[29] MT has shown potential benefits in treating addictions such as cigarette smoking by making the individual more aware, more open to experience, more flexible and more able to remain in the present moment instead of diverting attention to cigarette smoking as a form of experiential avoidance.[30] This is corroborated by a significant increase in the MAAS score in the MT group compared to the CT group in our study. Mindfulness techniques cultivate non-judgemental, non-reactive, present-centred attentional techniques. Moreover, there are additional benefits in increasing metacognitive awareness of cognition, emotion, experience, and perception.[31] This is consistent with mindfulness principles whereby we do not force the participants to resist the urge of smoking. Instead, we focus on improving self-control to handle the urge to smoke with flexibility by adopting mindfulness principles, without necessarily resorting to cigarettes.

Our study also observes a significant reduction in AAQ-2 scores among the participants in the MT group compared to the CT group. AAQ-2 measures the degree of psychological inflexibility and experiential avoidance.[24] This demonstrates that, in comparison to CT, MT not only encourages smokers to be more mindful but also encourages them to be more psychologically adaptable and receptive to psychological situations. This will help the smokers to accept difficult feelings or thoughts without them triggering smoking, but they will be more flexible to adopt different coping mechanisms. Furthermore, the literature indicates that smokers who avoid smoking-related distress or experiences are more likely to experience difficulties quitting, including pre-cessation risk factors (such as perceptions of greater barriers to successful cessation, perceptions of more failed prior quit attempts, perceptions of more severe problematic symptoms while quitting, and perceptions of more negative-reinforcing outcomes of smoking) and post-cessation outcomes (i.e., increased likelihood of cessation failure).[32,33]

One significant barrier to successfully quitting smoking is anxiety, which is a common withdrawal symptom throughout the cessation phase.[34] It can exacerbate withdrawal symptoms, boost smoking motivation, diminish the effectiveness of medication, and make it harder to stop smoking.[35] Also, those who fail to stop smoking while through a smoking cessation programme see a slight rise in long-term anxiety, which becomes a significant obstacle in subsequent attempts to stop.[36] As a result, managing anxiety is essential for a successful smoking cessation. According to our study, mindfulness practise can successfully reduce anxiety during quitting attempts. As a result, it is a helpful aid for those trying to stop smoking.

Stress is one of the obstacles to quitting smoking, according to studies.[37,38] This is due to the fact that numerous studies have found that smokers frequently smoke to relieve stress.[39–41] In addition, a study from Korea found a substantial correlation between stress levels and the inability of smokers to successfully quit,[37] suggesting that smokers who experience stress may find it difficult to stop and have a high risk of relapsing.[36,42,43] In order to increase the success rate of the smoking cessation programme, it is essential to address stress. Since our study was able to show that the MT group experienced a considerable reduction in stress compared to the CT group's fluctuating stress level during the smoking cessation phase. The observed fluctuating stress levels in the CT group may be attributed to various reasons, but it is widely recognised that during the early stages of smoking cessation or reduction, stress levels can rise due to the depletion of the pleasure sensation caused by nicotine. In contrast, the MT group appears to have effectively managed this stress effect, suggesting that MT is a more effective approach. Furthermore, MT has been shown in numerous studies to aid in stress reduction, which will be an important tool in addressing general mental health during the quitting smoking phase.[44,45]

According to previous research, depression is a common occurrence during smoking cessation programs, and there is a correlation between the two.[46] Even individuals who did not initially meet the criteria for major depression may experience worsened depression during the cessation phase.[47] Moreover, depression has been identified as a crucial predictor of successful smoking cessation, as individuals with

depression were found to have a lower likelihood of achieving smoking abstinence compared to those without depression.[48] Similarly, a 20-year longitudinal study reported that depressive symptoms were associated with a lower likelihood of smoking cessation over a long period.[49] In our study, we found that the MT group demonstrated a significant reduction in DASS-Depression compared to the CT group. Although both groups had normal scores on the depression scale at baseline, we noticed a gradual increase in scores in the CT group, possibly due to nicotine withdrawal symptoms. However, the MT group was able to effectively control their depression during the cessation period.

Overall, an online smoking cessation programme is a feasible and effective approach, as both groups show a promising reduction in the number of cigarettes smoked per day and nicotine reduction. Likewise, other studies have also proved that online-based smoking cessation interventions are effective in helping smokers to quit smoking.[50,51] One of the reasons for this success is that it breaks the burden of the clinical visit[51] which is a major barrier for smokers seeking help. Furthermore, they also can negate the feeling of being stigmatised and fear of failure in online smoking cessation programmes because they are not physically present. Feeling stigmatised causes failures in smoking cessation and results in dropouts from the programme.[52] Indeed, online therapy has its own set of challenges, including technical difficulties, distractions, interruptions, limited nonverbal cues, and scheduling difficulties. However, these challenges can be mitigated through careful planning and implementation of appropriate strategies. For example, the use of reliable software and equipment can help minimise technical difficulties. Additionally, providing participants with clear instructions on how to prepare their environment for online therapy sessions can reduce distractions and interruptions. Overall, while online therapy may present some unique challenges, with proper planning and implementation, it can be an effective alternative to traditional in-person therapy.

LIMITATION AND WAY MOVING FORWARD

Since the study relies on respondents filling out questionnaires, information bias could exist, especially when it comes to self-declared smoking abstinence. Therefore, as evidence of cessation, we can potentially add in future research one monthly trip to the closest quit-smoking clinic to have carbon monoxide (CO) levels measured. In a programme to help people stop smoking, a CO analyser can also be used as a motivating tool.[53] Additionally, due to the resource limitations, we could only concentrate on cigarette smokers and had to turn away 41 e-cigarette users. As a result, because contemporary generations prefer e-cigarettes over traditional tobacco cigarettes, we should include e-cigarette users in the upcoming study as well. In our study, time was also a constraint, so we were unable to conduct a long-duration study. Perhaps in the future, a longer follow-up could be conducted to acquire a better understanding of smokers' coping strategies for quitting.

CONCLUSION

While addressing one of the main barriers, mental health, online mindfulness treatment (MT) is more successful in assisting smokers in quitting compared to the present counselling therapy (CT) widely employed in all smoking cessation clinics in Malaysia. Despite the fact that we were not able to observe effectiveness of MT in achieving smoking abstinence, we were able to demonstrate the efficacy of online MT over CT in reducing the number of cigarettes smoked per day. This accomplishment goes hand in hand with addressing mental health by ensuring they are more alert, flexible, receptive to psychological events and capable of controlling stress, anxiety and depression. Furthermore, online therapy platforms provide significant benefits and are realistic, as both levels demonstrated a reduced number of cigarettes smoked per day. Finally, more follow-ups and research should be undertaken using online platforms to examine the effectiveness of larger-scale and longer-term MTs, especially regards to smoking abstinence.

AVAILABILITY OF DATA AND MATERIALS

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

COMPETING/CONFLICT OF INTEREST

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

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ORIGINAL ARTICLE

Empathy amongst doctors: an observational study

Thiruselvi Subramaniam, MMed (Anes)[1], Pavanam Sasha Valuyeetham, PsyD[2], Valuyeetham Kamaru Ambu, MSurg[3]

[1]International Medical University, Malaysia, [2]Cognitive Solutions Learning Center,Chicago, Ilinois, USA, [3]CMH Specialist Hospital, Seremban

ABSTRACT

Introduction: Empathy is the ability to put oneself in another's emotional space and experience what they feel. Either due to lack of experience or mundaness of practice, a state of empathy can become premised, and individuals become indifferent or detached. We aimed to explore the level of empathy among doctors at different levels of practice, age, gender, academics, non-academics and discipline.

Materials and Methods: This was a cross-sectional, observational study on empathy among doctors practicing in the private, public hospital sector and faculty at a medical university in Negeri Sembilan, Malaysia that utilised convenience sampling for data collection. The Toronto Empathy Questionnaire (TEQ) a validated tool was used to measure empathy.

Results: The questionnaire was completed by 127 doctors, 52% (n= 66) were males and 48% (n=61) females. There was no significant difference in empathy between male (M=46.44; SD=6.01) and female (M=45.05, SD=5.69) doctors; t (123) = 1.326, *p*=0.187. Pearson correlation coefficient was computed to assess the linear relationship between age and empathy and revealed no correlation between the two variables: r (125) =0.15, *p*=0.099. Medical-based doctors (M= 47.47, SD=5.98) demonstrated more empathy than surgical-based (M=44.32, SD=5.41); t (123) =-3.09, *p*=0.002. Those already specialised in their fields (M=47.38, SD=4.57) had more empathy than those who had not (M= 44.36, SD=6.52); t (123) =-2.96, p = 0.004. Doctors in the university (M=47.97, SD=4.31) tended to have more empathy than those in the public hospitals (M= 44.63, SD=6.27); t (117) =-2.91, *p*=0.004. Academicians had more empathy than non-academicians but there was no difference between those who were in clinical practice and not.

Conclusion: Our findings indicate that medical-based doctors demonstrate more empathy than surgical-based doctors, and there appeared to be no correlation between age and empathy. However, clinical experience and growth within the specialty seem to improve empathy. Doctors teaching in the university setting demonstrated more empathy than those practicing in the hospital setting.

Inclusion of empathy-related sessions in the undergraduate and post-graduate curriculum could bridge the gap in empathy noted with age, discipline, and experience in practice. Further research on empathy among doctors using a wider population in Malaysia and a TEQ questionnaire validated to the Asian population would provide better insight regarding this area of medical practice. Future research on outcomes of inclusion of programmes targeted at improving empathy to create awareness during practice would support patient satisfaction and safety.

KEYWORDS:
Empathy, medical education, gender, medical disciplines, age

INTRODUCTION

Empathy is a subjective feeling that is often underused and misunderstood yet important among professionals who work in the healthcare industry The origin of the word *empathy* dates back to the 1880s, when German psychologist Theodore Lipps coined the term "einfuhlung" (literally, "in-feeling") to describe the emotional appreciation of another's feelings. Empathy has further been described as the process of understanding a person's subjective experience by vicariously sharing that experience while maintaining an observant stance.[1]

Edward Bradford Titchener, a British Psychologist is credited for translating the German term from "Einfühlung" (or "feeling into") to Empathy in 1909.[2,3] Empathy, in layman's term, is described as the ability to "put oneself into another person's shoes" or feel another person's affect or emotional experience. Empathy does not have a precise definition and is understood differently by people. Keen stated that empathy means to recognise others' feelings the causes of those feelings, and to be able to participate in the emotional experience of an individual without becoming part of it.[4] Halpern has a slightly different description for the term empathy as being seen as a skill learned or an attitude of life, which can be used to try to come into contact with someone, to communicate and understand others' experiences or feelings.[5]

Empathy is partly underpinned by the Social Learning Theory (SLT) introduced in the 1960s by Albert Bandura that developed into Social Cognitive Theory (SCT) in the eighties, which propounds that learning occurs in a social context when there is a continued complementary relationship/ exchange between an individual, environment and behaviour.[6]

The level of empathy expressed varies across different professions, especially between the blue- and white-collar

This article was accepted: 14 May 2023
Corresponding Author: Thiruselvi Subramaniam
Email: thiruselvi_subramaniam@imu.edu.my

professions. One research identified general physicians to score higher on empathy, warmness and genuineness compared to other nonmedical professions such as lawyers and clergymen.[6,7] Expressing empathy in the health care field is very important to ensure patient satisfaction and positive health outcome. However, it has come to attention that the level of expressed empathy varies across different professions in the medical field perhaps even from undergraduate medical period.[8,9] There is also scarcity of research about empathy among practicing doctors in the local context compared to the same among medical students. There is a need to identify the time and areas where changes can be implemented to improve empathy among not just junior doctors but doctors at large. Hence, identifying level of empathy as a start towards something more defined would be important.

Literature search resulted in more research regarding empathy and medical undergraduates than those of the practicing doctors or post-graduates in Malaysia. This study aims to explore the level of empathy expressed by doctors at different levels of practice, age, gender, academic stand, level of practice and state of clinical practice. Several tools are available to measure the level of empathy like Jefferson Scale of Physician Empathy (JSPE), Toronto Empathy Questionnaire (TEQ), Therapist Empathy Scale (TES) and many more. However, a recent systematic literature review and meta-analysis of the past 10 years on assessment instruments and psychometric quality did not find a gold standard questionnaire to assess the level of empathy.[10] We chose to use the TEQ with permission as it had the items we were interested in and easy to complete in a short time, considering the busy schedules of the clinicians that participated in the research.

MATERIALS AND METHODS

This is a cross-sectional, observational study involving doctors in the private sector, public hospital and a medical university in Seremban, Negeri Sembilan, Malaysia. Convenience sampling method was employed to collect data over 4 months from February to May 2017. Questionnaires were distributed directly and through peers to doctors in these respective places.

The TEQ, available online, measures an individual's emotional ability to understand and respond to others. It was originally developed in English and takes 5–7 minutes to complete. The TEQ which is a self-report containing 16 items, each rated on a 5-point Likert scale from 'never' to 'often' was used as our measuring tool for empathy. Positively worded item [1, 3, 5, 6, 8, 9, 13 and 16] responses are scored as Never = 0; Rarely = 1; Sometimes = 2; Often= 3; Always = 4; so higher the scores the higher the level of empathy. Negatively worded items [2, 4, 7, 10 - 12, 14 – 15] are reversed and scored to get the same results. Higher scores indicate a higher level of empathy.[11]

This questionnaire was developed by reviewing other empathy instruments and found to be positively correlated with measures of social coding and other empathy measures. It has been proven to have high internal consistency, construct validity and test–retest reliability through the correlation with other tools of empathy like Empathy Quotient and Autism Quotient; the internal consistency, α=0.85 to α=0.87 and high test–retest reliability, r=0.81, p<0.001.[11]

The questionnaire was given out to doctors practicing in the public hospitals, private hospital, practicing as well as teaching and those who had stopped clinical work and were only involved in teaching. Doctors from all levels of practice were invited to participate in the study and ranged from house officers to specialists.

All participants were grouped; (1) by age, (2) discipline (surgical-based and medical-based), (3) state of clinical practice (clinically active and clinically inactive), (4) level of practice (broadly classified as specialists and non-specialists) and (5) academic stand (academician and non-academician) (6) Practice sector (private, public and university). We identified academicians as those who spent all or almost all their time teaching. Doctors who were clinically active and practicing in the hospitals were identified as non-academicians.

The disciplines categorised under Medical-based were Internal medicine, Radiology, Family Medicine, Psychiatry, Pediatrics, Emergency Medicine, Rehabilitation Medicine, Anesthesia & Critical Care and Dermatology and Surgical-based were Surgery, otorhinolaryngology, Ophthalmology, Obstetrics & Gynecology and Orthopedics. House officers and medical officers were also categorised accordingly depending on the departments they were attached to at the time of data collection.

The questionnaires were handed out to the participants personally and were collected. For those who did not respond to emails immediately, the questionnaires were sent to their place of practice and given time to revert.

Inclusion Criteria

Doctors working in the public and private hospital as well as those working in a university in Seremban, Negeri Sembilan, Malaysia who completed the TEQ questionnaire were included in the study.

Exclusion Criteria

Healthcare workers like nurses, medical assistants and others were excluded from the study.

Data Analysis

All personal information collected were kept safe and confidential by the principal investigator in a password safe folder. Data were collected and analysed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. A test of normality was carried out on the distribution of the TEQ scores, and independent t-test and Pearson's Correlation Coefficient were used to analyse the data. The result was considered significant if the p value was found to be less than 0.05.

Ethical Approval

The proposal was submitted, and approval was obtained from the medical research and ethical committee, Ministry of Health; NMRR-16-1376-31345-(IIR).

RESULTS

The TEQ was completed by 127 doctors from the university(n=37), public (n=84) and private sector (n=6), of whom 52% (n= 66) were males and 48% (n=61) females. A test for normality of data distribution using the Shapiro-Wilk test was performed (W=0.986, *p*=0.217) and an independent t-test was conducted to analyse the empathy scores of the participants. However, there was missing information in some of the questionnaires accounting for differences in the total numbers (n=125 and n=124) for some of the sub-groups, respectively. Mean TEQ scores for doctors from private, public hospital and university were 48.17 (SD=4.07), 44.63 (SD=6.27) and 47.97(SD=4.31) respectively. Empathy was compared between the participants from university and public hospitals (n=119) as the number of participants from private hospitals was small (n=6).

Significant differences were noted in the sub-groups that were discipline-based, at level of practice, practice sector and academic stand. No statistically significant difference was identified for state of clinical practice and gender (Table I).

The TEQ consisted of 16 items and the reliability analysis of the items for this research resulted in Cronbach's Alpha, α=0.727. The overall mean of the total TEQ score for the doctors was 45.8 (SD=5.87), out of a maximum score of 64. The descriptive analysis of the scores for each item can be found in Table II.

The mean values for age appear to show that empathy increases with age but Pearson correlation coefficient computed to assess the linear relationship between age and empathy revealed no statistically significant correlation between the two variables: r (125) =0.15, *p*=0.099.

DISCUSSION

General Observation

Studies have looked at empathy and gender differences, various disciplines, age, race and changes with time. There is evidence of a decline in empathy that begins during the clinical years of medical school, which continues throughout residency training.[8,9,12-16] However, the findings are not consistent, as some report no change and even improvement in empathy as students progress through medical school.[17-20] Perhaps the different tests used as measurement tool and other factors like culture, environment, and curriculum strategies may be influencing factors. We did not compare scores from our research with other studies as the screening tools were not the same.

Stratta et al explored empathy in medical students and qualified doctors and participants identified that there was an empathy decline in themselves and their colleagues.[21] Stressful working environments, the prioritisation of patients' physical rather than psychological well-being, and the attitudes of senior colleagues were all suggested as possible causes. The Francis Report mentioned several reasons for the declining empathy among the healthcare personnel, namely compassion fatigue, overwork, excess demand, lack of continuity and failure to see the patient as a fellow human being.[22-23] It is reasoned that empathy is a skill that if included in the undergraduate and post-graduate curricula may mitigate the decline in empathy among doctors.[8,21]

We acknowledge that there are limitations as the TEQ was designed based on the western culture, primarily focuses on cognitive empathy without addressing the affective empathy and does not include the other nuances in empathy like intensity as well as appropriateness. However, another similar study conducted locally on empathy among medical students found the TEQ instrument valid and reliable for local Malaysian context.[16]

Age and Gender Differences

In our study, the mean values for age appeared to show that empathy increases with age though the Pearson's Correlation showed that age's effect on empathy was not significant. Contrary to our finding, increasing age has been shown to have a positive correlation with level of empathy both among non-surgical and surgical specialists.[24] Beadle et al in their review paper on impact of ageing on empathy had mixed findings in the literature on empathy and ageing, which they suggested could be related to methods used to study empathy. The inconsistent results they suggested could be due to inconsistent sample sizes, unequal numbers of men and women, and reduced capacity to generalise across cultures.[25] Our results could possibly be influenced by these factors as well, as our study population was only from one state in the country.

The majority of research reported that females, whether medical students, junior or senior doctors, were considerably more empathetic than their male counterparts.[8,12-15,26-33] Being female, married, and having children appeared related to higher empathy. Researchers suggest that females have more oxytocin, which promote emotional empathy while males have more testosterone, that inhibit empathy, while others explain the observed gender differences as being largely due to cultural expectations about gender roles.[34-36] Christov et al identified that there are social, contextual and cultural influences that influence the observed behavioural and neural differences in affective empathy between males and females. They also suggest that males vary more than females in some aspects of emotional processing and altruistic behaviour, and they appear to be less empathetic because of their higher discrimination in targeting helping behaviour whereas females appear more indiscriminately empathetic.[35]

Contrary to other research findings, our results did not reveal significant gender differences which were similar to some research.[24,37-38] Our findings may be as a result of a smaller sample size or that both female specialists and female non-specialists were grouped together for analysis. Specialists generally have been found to have higher empathy scores than non-specialists.[39]

Within the male population, using the Jefferson Scale of Physician Empathy (JSPE), it was found that male psychiatrists scored significantly higher than male surgeons.[40] However, this could be that male psychiatrist are non-surgical and research already show that non-surgical clinicians have more empathy than their surgical colleagues.

Table I: Comparison of differences in TEQ scores in the various sub-groups (discipline-based, state of clinical practise, level of practise, academic stand, practice sector and gender)

Groups	Total respondents	Mean TEQ score	Standard deviation	t	df	*p* value
Surgical based (n= 68)	125	44.32	5.410	-3.090	123	0.002
Medical based (n=57)		47.47	5.982			
Specialist (n=58)	125	47.38	125	-2.958	123	0.004
Non-specialist (n=67		44.36	6.515			
Clinically active (n=114)	125	45.75	5.982	0.088	123	0.930
Inactive clinically (n=11)		45.91	4.784			
Academicians (n=42)	124	47.55	4.522	-2.494	122	0.014
Non-academicians (n=82)		44.82	6.307			
University (n= 36)	119	47.97	4.306	2.914	117	0.004
Public Hospital (n=83)		44.63	6.270			
Female (n= 61)	127	45.05	5.69	1.326	123	0.187
Male (n= 66)		46.44	6.01			

Table II: Descriptive statistics of the TEQ items in this study

Items		N	Minimum	Maximum	Mean	Std. Deviation
1.	When someone else feels excited, I tend to get excited too	127	0	4	2.22	0.796
2.	I remain unaffected when someone close to me is happy	127	0	4	2.36	0.861
3.	It upsets me to see someone being treated disrespectfully.	127	0	4	3.40	0.789
4.	I remain unaffected when someone close to me is happy	127	0	4	2.91	0.836
5.	I enjoy making other people feel better	127	0	4	3.36	0.742
6.	I have tender, concerned feelings for people less fortunate than me	127	1	4	3.16	0.717
7.	When a friend starts to talk about his/her problems, I try to steer the conversation towards something else	127	0	4	2.91	0.801
8.	I can tell when others are sad even when they do not say anything	127	1	4	2.66	0.737
9.	I find that I am "in tune" with other people's moods	127	0	5	2.23	0.789
10.	I do not feel sympathy for people who cause their own serious illnesses	126	0	4	2.44	0.976
11.	I become irritated when someone cries	127	0	4	3.04	0.877
12.	I am not really interested in how other people feel	126	0	4	3.05	0.818
13.	I get a strong urge to help when I see someone who is upset	127	0	4	2.88	0.860
14.	When I see someone being treated unfairly, I do not feel very much pity for them	127	0	4	3.21	0.860
15.	I find it silly for people to cry out of happiness	127	0	4	3.09	0.877
16.	When I see someone being taken advantage of, I feel kind of protective towards him\her	127	0	4	2.81	0.843
	Valid N	125				

*Questions 2, 4, 7, 10, 11,12, 14 and 15 were recoded to reverse.

Following on, within specialty, female physicians had higher empathy scores than male physicians.[32]

State of Specialisation and Empathy

There is evidence that there is a negative correlation between empathy and burnout.[39,41] Our research showed that specialists demonstrated significantly more empathy than non-specialists (p=0.004). This was similar to research by Fereira et al who found a significant difference in Maslach Burnout Inventory (MBI) subscale scores (emotional exhaustion, depersonalisation, and lack of personal accomplishment) between residents and specialists.[39] Specialists, though bear more responsibilities, are more secure in their profession and may have more time to spend and thus empathise with their patients. Non-specialists, not settled in their specialisation, generally in-charge of all the tasks in the wards, with more stay in calls have relatively less time to spend with patients and face burnout more than those already specialised.

Commonly, progressing on to specialisation in a clinical field takes time and most are older by the time they do. Hence may explain the positive correlation between age and state of specialisation and level of empathy. However, there appears to be no correlation between the number of years of experience working as a doctor and the level of empathy.[24]

Surgical and Medical Disciplines

Our results showed that the clinicians from the medical-based disciplines demonstrated more empathy than the surgical-based clinicians (p=0.002). The results were similar to a few other studies, one being by Walocha et al who grouped physicians into surgical: non-surgical and found that non-surgical specialists displayed a higher level of empathy than their surgical counterparts.[24]

A review on empathy and its importance as it pertains to the surgeon–patient relationship and improving patient outcomes reported that there was a decline that began at clinical school.[9] According to them, surgeons are particularly susceptible to the decline in empathy as they move through their training and attribute it to lack of inclusion of empathy skills training within the surgical training program. They believe that empathy can be taught.

In a study by Hojat et al with control for gender, psychiatrists scored a mean empathy rating that was significantly higher than that of other physicians (anesthesiology, orthopaedic surgery, neurosurgery, radiology, cardiovascular surgery, obstetrics and gynecology and general surgery).[26]

Academicians and Non-Academics

As mentioned earlier, we identified academicians as those who spent all or almost all of their time teaching. Doctors who were clinically active and only taught a few sessions a week were identified as non-academicians. Academicians had higher empathy scores than non-academicians. Non-academicians being clinically active were challenged by factors that influenced their level of empathy like doctor–patient ratio within a period in the clinics, dealing with ward rounds and challenges of being on active calls, lack of sleep and many others. Academicians spend more time teaching and generally are not caught in the web of clinics, high patient load, procedures, ward work, call duties and the stress of juggling all these with teaching. They generally spend time with a smaller number of patients selected for discussions with students, thus being able to spend time and empathise with each patient.

Lustig in his letter to editor about Haslam's paper titled: the overview of the role of empathy in medicine, aptly summarised that "empathy is not an optional extra but a clinical competence essential for sound medical practice, no matter what our specialty. All clinical practice requires a doctor–patient relationship, the core skill of which is empathy".[42,43]

CONCLUSION

Our findings indicate that medical-based doctors demonstrate more empathy than surgical-based doctors. There appeared to be no correlation between age and empathy. However, clinical experience and growth within the specialty seem to improve empathy. Doctors teaching in the university setting demonstrated more empathy than those practicing in the hospital setting.

Inclusion of empathy-related sessions in the undergraduate and post-graduate curriculum could bridge the gap in empathy noted with age, discipline and experience in practice. Further research on empathy among doctors using a wider population in Malaysia and a TEQ questionnaire validated to the Asian population would provide better insight regarding this area of medical practice. Future research on outcomes of inclusion of programmes targeted at improving empathy to create awareness during practice would support patient satisfaction and safety.

LIMITATIONS

- We acknowledge that there are limitations as the TEQ was designed based on the western culture, primarily focuses on cognitive empathy without addressing the affective empathy and does not include the other nuances in empathy like intensity as well appropriateness.
- A larger sample with more representation from the private sector would have been preferable, but there were challenges due to logistics, like availability of doctors, especially in the public and private hospitals, due to their busy schedules.
- The population involved was from one state in the country.

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ORIGINAL ARTICLE

Anti-hypertensive prescription practices in private hospitals in Malaysia: a prospective, non-interventional, observational study

Ng Wai Kiat, FRACP[1], Ashok Zachariah Philip, MRCP[2], Lim Thien Thien, MD[3], Wong Ming, MRCP[6], Goh Eng Leong, MD[4], Tengku Saifuddin Tengku Ismail, MRCP[5], Goh Teck Hwa, FRCP[4]

[1]Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, [2]Mahkota Medical Centre, Melaka, Malaysia, [3]Island Hospital, Penang, Malaysia, [4]Loh Guan Lye Hospital, Penang, Malaysia, [5]KPJ Tawakkal Specialist, Kuala Lumpur, Malaysia, [6]Sunway Medical Centre, Selangor, Malaysia

ABSTRACT

Introduction: In managing hypertension, monotherapy and sometimes a combination of more than one agent are used to achieve blood pressure (BP) control. The objective of this prospective, observational, multi-centre study was to assess the level of BP control in patients receiving one or more anti-hypertensive drugs in private medical centres in Malaysia according to the treatment regimens (monotherapy, free drug combinations and single pill combinations).

Materials and Methods: Data were collected through medical records and interview sessions with patients on current pharmacotherapy for hypertension management at baseline and 2–3 months later. Results are expressed as mean ± SD for continuous data and as frequencies and percentages for categorical data.

Results: Among 182 recruited patients, 89 (49%) achieved BP control by the end of the study. Majority (62/89) patients were on single-pill (monotherapy or SPC) anti-hypertensives. Majority (63/89) required more than two anti-hypertensives to achieve BP control.

Conclusion: Both SPC and free drug combination anti-hypertensives reduced BPs, but physicians preferred SPC to improve BP control and increase treatment compliance.

KEYWORDS:
Systolic pressure, diastolic pressure, pharmacotherapy, tablet, therapeutic adherence and compliance, epidemiological monitoring, multicentre studies

INTRODUCTION

The prevalence of hypertension in Malaysia has been on the rise. According to the 2019 National Health and Morbidity Survey, about 3 in 10 people or 6.4 million in Malaysia had hypertension.[1] However, only half of them were aware of their condition. And among those who were on medication, only 45% had their blood pressure (BP) under control. These problems need to be urgently addressed as hypertension is one of the leading preventable causes of premature death worldwide. It is believed to result in 7.5 million deaths (12.8% of deaths due to all causes) and 57 million disability-adjusted life years (DALYS) which is 3.7% of total DALYS.[2]

Hypertension is primarily managed through pharmacotherapy. The anti-hypertensive drugs belong to various classes according to their unique mechanism of action. Monotherapy and sometimes a combination of more than one agent are used to achieve BP control. Studies have assessed the effects of combination therapy in achieving and maintaining BP goals as per clinical practice guidelines.[3,4]

In Malaysia, clinical practice guidelines are regularly updated for guiding physicians on current anti-hypertensive goals and therapies. Physicians play a major role in putting these recommendations into clinical practice. In a study in a tertiary hospital in Malaysia, about 67% of the patients received guidelines-compliant pharmacotherapy.[5] In another study, doctors' knowledge of hypertension guidelines and their prescription practices were analysed, and about 73% were noted to have adequate knowledge of current guidelines.[6] Despite these encouraging results, there are still gaps between guideline recommendations and actual practice.[6]

The objective of this study was to assess the level of BP control in patients receiving one or more anti-hypertensive drugs in private medical centres in Malaysia, depending on the number and type of regimen of anti-hypertensive treatments used.

MATERIALS AND METHODS

Study Design

This prospective, non-interventional, observational study involved outpatients who were seen and treated by physicians (cardiologists or other specialists) in 18 private medical centres throughout Malaysia between January and November 2019.

The participating physicians were asked to establish and continue care and treatment according to their current medical practice. They were free to initiate any form of treatment according to their own medical decision and could initiate a single-pill strategy as mentioned by the guidelines.

This article was accepted: 14 May 2023
Corresponding Author: Ng Wai Kiat
Email: ngwaikiat@gmail.com

No specific analysis or specific treatment introduction was required. As the objective of the study was focussed on the number of anti-hypertensive agents, the class and doses of these agents were not reported.

The study was performed in compliance with the requirements of the International Conference of Harmonization and Good Clinical Practice. The study gained full regulatory approval from Malaysia's Medical Research Ethics Committee on 8 November 2018.

Study Participants
Participants were adult outpatients (age >18 years) of either gender who were on at least one anti-hypertensive medication and were seen and treated by physicians from private medical centres in Malaysia. Patients hospitalised for cardiovascular diseases in the last 3 months (including revascularisation) were excluded.

All participants provided written informed consent. Patients were free to withdraw from the study at any time without giving a reason. They were also told that there would be no negative consequences for withdrawing from the study. The treating physician could also withdraw patients from the study if they deemed it appropriate for safety or ethical reasons or if it was detrimental to the well-being of the patient.

Due to the study design and objectives, a formal sample size calculation was not performed. About 320 total patients were estimated from the initially planned 32 physicians (based on clinical practice history of ten patients per physician). However, due to the busy schedule of the investigators, only 18 investigators participated.

Data Collection
Data were collected through medical records and interview sessions with the patient on current pharmacotherapy for hypertension management at baseline and at 3-month follow-up (according to the International Society of Hypertension 2020 Hypertension Guideline's recommendation for monitoring BP control).7 The names of the patients were blinded to prevent bias.

Clinical information such as patient demographics, systolic blood pressure (SBP)/diastolic blood pressure (DBP) values, anti-hypertensive treatment details, concomitant diseases, and BP control status were collected at baseline and subsequent visit (within 2–3 months).

No investigational products were assessed for safety or efficacy.

Statistical Analysis
Results were expressed as mean ± SD for continuous data and as frequencies and percentages for categorical data. All descriptive statistics were carried out using STATA, version 13.

RESULTS

Baseline Demographic and Other Patient Characteristics
From a planned sample size of 320 patients, 207 (from 18 centres) met the eligibility criteria and were recruited into the study. Six of these centres recruited between two and nine patients each, while the remaining centres recruited more than ten patients each (11 patients [n=1], 13 patients [n=1], 15 patients [n=8], 16 patients [n=1], and 17 patients [n=1]).

By the end of the study, 25 patients were lost to follow-up. The final analysis included 182 patients.

The patients ranged from 23 to 81 years old (mean age of 52.9 years [SD 12.5]) (Table 1). Majority of the patients were between the ages of 30 and 60 years old, with the most common age group being the 50–60 years group (34%). Among the patients, 44% were Chinese, followed by 42% Malay, and 8% and 5% Indian and other races, respectively (Table I). The study population comprised an almost equal proportion of males and females (53% and 47%, respectively). More than half (62%) had primary/secondary education.

At baseline, patients generally had a healthy mean body mass index (BMI) of 28.27 (SD 6.54) (Table I). The most common concomitant diseases were dyslipidaemia (38%) and diabetes (26%) (Table I).

Anti-hypertensive Treatment
At baseline, patients in the study were on at least one type of anti-hypertensives with 43% on monotherapy (one agent), 23% on free drug combinations (more than one agent in multiple loose pills) and 29% on SPC of dual or triple therapy (2 or 3 agents in a single pill) (Table II).

According to the physicians, 65% and 32% of the patients were suitable for SPC dual and triple therapies, respectively, to improve BP control, treatment compliance, and cardiovascular risk management. At the 3-month assessment, most patients had either the same (64%) or higher (32%) number of anti-hypertensives prescribed from baseline. Most patients were on two or more anti-hypertensive treatments (74%) (Table II). By the end of the study (month 3), there was increased use of SPC (42%) compared to baseline (29%), and a slight increase in the use of free drug combinations (32% versus 28% at baseline). However, the use of monotherapy reduced by month 3 (43% versus 26% at baseline) (Table II).

Blood Pressure Control
Over the course of the study, there was a reduction in BPs of the study participants (SBP by 10 mmHg and DBP by 5 mmHg) (Table II).

The BP reduction varied with the number of anti-hypertensives prescribed. Patients who had an increase in the number of anti-hypertensives showed an average reduction in SBP of 19 mmHg and DBP of 10 mmHg, while patients who had a decrease in prescribed anti-hypertensives had a reduction in SBP of 2 mmHg and increase in DBP of 4 mmHg. Patients who had no change in anti-hypertensive medication registered a decrease of 5 and 3 mmHg, respectively, for SBP

Table I: Demographics and baseline characteristics of adult outpatients with hypertension

Patient characteristics	N = 182
Age, years	
Mean (SD)	52.9 (12.5)
Median (IQR)	53.5 (44, 59)
Min, Max	23, 81
Age group (years), n (%)	
<30	2 (1)
30–<40	27 (15)
40–<50	47 (26)
50–<60	61 (34)
60–<70	22 (12)
≥70	23 (13)
Gender, n (%)	
Male	97 (53)
Female	85 (47)
Race, n (%)	
Malay	77 (42)
Chinese	80 (44)
Indian	15 (8)
Others	10 (5)
Education level, n (%)	
Primary/Secondary	113 (62)
Diploma	32 (18)
Degree	28 (15)
Others	9 (5)
Height, cm	
Mean (SD)	163.2 (8.7)
Median (IQR)	164 (156, 169)
Min, Max	142.5, 184
Weight, kg	
Mean (SD)	75.4 (19.0)
Median (IQR)	73.8 (63.9, 83.0)
Min, Max	40.5, 193.4
BMI, kg/m^2	
Mean (SD)	28.3 (6.5)
Median (IQR)	27.2 (24.6, 30.2)
Min, Max	16.0, 71.9
Concomitant diseases, n (%)	
Diabetes	74 (26)
Renal disease	22 (8)
Dyslipidaemia	108 (38)
Ischaemic heart disease	18 (6)
Cerebrovascular disease	20 (7)
None of the above	43 (15)

BMI, body mass index; IQR, Interquartile range; SD, standard deviation

and DBP. Patients on SPC and free drug combination medications registered a decrease in systolic and diastolic BPs except for free drug combination of two anti-hypertensives where diastolic BPs increased (Figure 1). However, only patients on SPC-dual therapy registered a lowering of SBPs to below 140 mmHg.

Only 89 patients (49%) of the patients reached BP target levels of below 140/90 mmHg by the end of the study (Table 2). Among the 89 patients who reached BP control, more than two-thirds (62 out of 89) were on single pill (including monotherapy, SPC 2 and 3 drugs) while the rest were on multiple pills (Figure 2). Close to three-fourths of the patients (71%) needed a minimum of two or more anti-hypertensive agents to reach BP control.

For dual therapy, more patients on SPC (55%) achieved BP control than those on free drug combination (47%). However, for triple therapy, more patients on free drug combination (38%) achieved BP control than those on SPC (22 %).

Treatment Compliance

According to patient responses, compliance to treatment was moderate at baseline and improved to good at the final visit. By the end of the study, fewer patients reported having ran out of medications (5% versus 95% at baseline), forgetting to take their medications (5% versus 7% at baseline), or taking their medication later than the usual time (29% versus 43% at baseline).

DISCUSSION

This observational study aimed to explore the prescription practices of doctors in private medical hospitals and achievement of adequate BP control in patients in Malaysia. The results found that based on physicians' perception, BP

Table II: Anti-hypertensive treatments and BP control of adult outpatients with hypertension

Patient characteristics	Baseline (n=182)	At 3 months (n=182)
Anti-hypertensive treatment		
Number of anti-hypertensive treatments, n (%)		
1	79 (43)	47 (26)
2	62 (34)	73 (40)
3	31 (17)	47 (26)
≥4	10 (6)	15 (8)
Type of medication prescribed, n (%)		
Monotherapy	79 (43)	47 (26)
Free drug combination pills	50 (28)	59 (32)
Only SPC	53 (29)	76 (42)
BP control		
SBP, mmHg		
Mean (SD)	149.3 (20.9)	139.6 (16.8)
Median (IQR)	147.5 (133, 160)	137 (130, 150)
Min, Max	102, 210	101, 190
DBP, mmHg		
Mean (SD)	87.2 (12.7)	81.6 (9.9)
Median (IQR)	88.0 (80, 96)	80.0 (77, 89)
Min, Max	53, 120	58, 115
BP < 140/90 mmHg, n (%)	55 (30)	89 (49)*
BP ≥ 140/90 mmHg, n (%)	127 (70)	93 (51)

BP, blood pressure; DBP, diastolic blood pressure; IQR, Interquartile range; SD, standard deviation; SBP, systolic blood pressure; SPC, single-pill combination
*p<0.0001

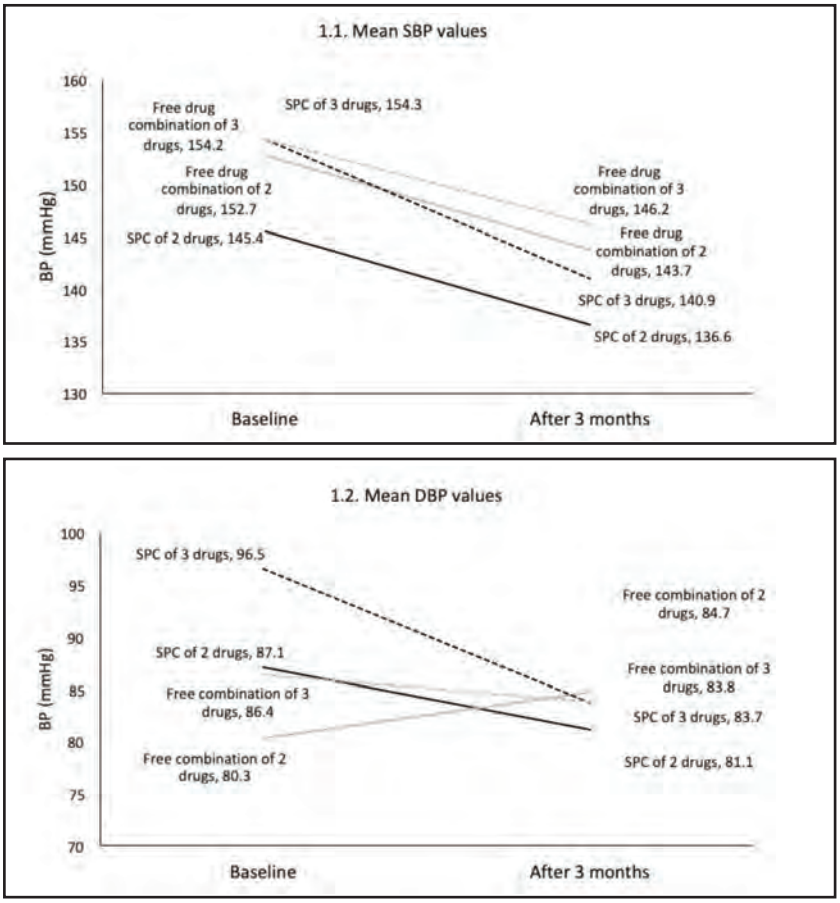

Fig. 1: Blood pressure values for adult outpatients with hypertension on SPC versus free drug combination anti-hypertensive treatments

Number of patients	Baseline	After 3 months
SPC of 2 drugs	48	58
Free drug combination of 2 drugs	14	15
SPC of 3 drugs	4	18
Free drug combination of 3 drugs	27	29

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPC, single-pill combination

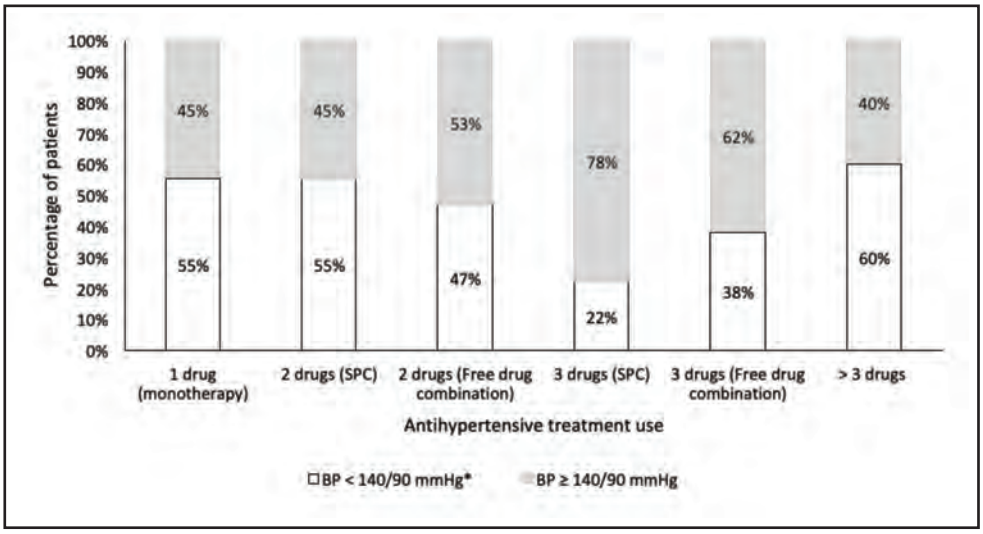

Fig. 2: Blood pressure control of adult outpatients with hypertension after 3 months of treatment based on anti-hypertensive medication regimens

Number of patients	1 drug (monotherapy)	2 drugs (SPC)	2 drugs (Free drug combination)	3 drugs (SPC)	3 drugs (Free drug combination)	>3 drugs
BP ≥ 140/90 mmHg	21	26	8	14	18	6
BP < 140/90 mmHg*	26	32	7	4	11	9

BP, blood pressure; SPC, single-pill combination
*p=0.11

results, and patients' response, SPC regimens improved BP control and increased treatment compliance.

Earlier studies revealed gaps in local healthcare practices for hypertension management. According to the 2014 National Medical Care Survey, private primary care healthcare settings in Malaysia do not perform as well as the public sector in treating chronic conditions and prescribing practices.[8] Another study revealed suboptimal prescription practices in both public and private primary care clinics in the country.[9] In our study, only half of the patients achieved target BP control and majority of the patients required more than two anti-hypertensives to achieve BP control. Our results showed good BP control with more than one anti-hypertensive agent in contrast to another study on hypertension management in public primary care clinics in Malaysia, which showed a negative association between two or more anti-hypertensives and good BP control.[10] However, there is an observed difference in the age groups, sex distribution, and ethnicity between both studies. Our study had a younger population (76% ≤ 60 years versus 61.6% < 65 years); more males (53% versus 39.6%); and fewer patients of Malay ethnicity (42% versus 66%). The use of more than one anti-hypertensive agent for patients who did not achieve target BP levels was in line with guidelines.[11]

Our study also specifically looked at the efficiency of anti-hypertensive control in patients taking more than one anti-hypertensive medication as free drug combination versus SPC therapy. The physicians in our study felt that majority of the patients would benefit from a SPC regimen primarily for BP control. The results showed that although free combination anti-hypertensive treatments did reduce BPs, SPC of two drugs reduced SBP to target levels of below 140 mmHg. This was consistent with international guidelines, which recommend SPC for patients with BP of ≥140/90 mmHg or for patients with more than 20/10 mmHg above the BP goal.11 However, our study showed that those on free drug combination triple therapy had better BP control than SPC triple therapy. Nevertheless, another study showed that SPC with three drugs reduced BP better than free drug combination of three drugs.[12]

By the end of the study, there was increased use of SPC and free drug combinations. Physicians in our study felt that other than BP control, SPC would improve treatment compliance. Consequently, by the end of the study, patients reported being more compliant with their treatment. In addition, multiple other studies showed that SPC improved compliance compared to free drug combinations.[11,13] Another reason cited by the physicians for recommending SPC was to achieve better cardiovascular risk management. This is imperative as about 7.5 million cardiovascular deaths globally are due to hypertension[2] and studies showed that cardiovascular risk reduction can be achieved through control of BP.[14-16]

The strength of our study lies in its real-world design, which provides valuable information on treatment practices and patient characteristics. The study is focussed on patients attending private healthcare centres, which are not often captured in studies. Patients who attend private healthcare settings in the country are usually those who can afford the higher cost of medications which are covered by insurance or paid out-of-pocket.[17] Private healthcare patients may benefit from longer consultations, with more time for education and advice.[17-19] In addition, as this study involved multiple centres,

it may be a good reflection of private healthcare practices in the country. Furthermore, due to the prospective design, the study reflected more recent practices which would not have been captured with a retrospective study. Other studies on anti-hypertensive prescription practices have used similar prospective, observational designs.[20,21]

However, our study had several limitations. Firstly, the focus of this study is private hospitals, which only cater for about 2.1% of patients with hypertension in Malaysia.[22] Although the findings of this study represent a small segment of hypertension care in the country, there are differences in primary care service delivery between public and private sectors in Malaysia,[23] of which are important to capture. Secondly, the study did not include information on the drug classes and doses, duration of the disease, and when the treatment the patient was on was initiated. Nevertheless, our focus was treatment regimen (SPC or free dose combinations) and the inclusion of multiple variables may require a bigger sample size. Thirdly, our relatively small sample size and short follow-up may not adequately assess a chronic condition such as hypertension. Changes in therapy take a long time to affect the condition. And finally, the treating physician could withdraw patients from the study if they deemed it appropriate for safety or ethical reasons or if it was detrimental to the well-being of the patient. This was, however, inevitable due to the study being non-interventional and observational. This was also common for studies on prescription practices. In a meta-analysis on medication nonadherence in adult hypertensive patients, only two of the 28 studies included were interventional studies.[24]

CONCLUSION

This study showed that both SPC and free combination anti-hypertensive treatments reduced BPs. The SPC-dual therapy reduced systolic hypertension to lower than 140 mmHg (the target level of SBP) to achieve optimum health. In addition, the convenience of taking two different medications in a single pill would improve treatment compliance. Nevertheless, based on physicians' opinion, number of study subjects studied, and the duration of the study, the outcomes do not give a clear direction. Further studies may be required to elucidate the impact of prescription practices in the management of hypertension in Malaysia.

ACKNOWLEDGMENTS

We thank the following individuals for their expertise and assistance throughout the study:
Dr Low Eng Joo from Lam Wah Ee Hospital (Penang), Dr Nor Hayati Shaharuddin from Pantai Hospital Ayer Keroh (Melaka), Dato Dr Mahendra Raj from Pantai Medical Centre (Kuala Lumpur), Dr Yew Shiong Shiong from Mahkota Medical Centre (Melaka), Dr Lakshumanan Sanker from KPJ Specialist Selangor Centre (Selangor), Dr Jasminder Kaur from KPJ Tawakkal Specialist (Selangor), Dr Na Boon Seng from Loh Guan Lye Specialist Centre (Penang), Dr Raja Kumar Menon from KPJ Selangor Specialist Hospital (Selangor), Dr Tuan Jiun Haur from Penang Adventist Hospital (Penang), Dr Gan Hwa Wooi from Gleneagles Penang (Penang), and Dr Evelyn Chan from Penang Adventist Hospital (Penang).

The authors and investigators received investigator fees from Servier (M) Sdn Bhd for this study but the company had no role in the data collection, analysis, interpretation, and preparation of the manuscript.

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Implementing primary eye care in private practises in Malaysia: the challenges faced by optometrists

Nurul Ain Yahaya, Msc[1], Azuwan Musa, PhD[2], Mohd Zulfaezal Che Azemin, PhD[1], Nor Azlina A. Rahman, M.Comm, Med[1]

[1]Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Kuala Lumpur, Malaysia, [2]Kulliyyah of Medicine, International Islamic University Malaysia, Kuala Lumpur, Malaysia

ABSTRACT

Objective: In Malaysia, optometrists' role in the private sector is limited compared to their counterparts elsewhere. Primary eye care (PEC) is still not widely offered in private practises despite its demand to reduce the public's eye morbidity. This study aims to explore the challenges perceived by the private sector optometrists in implementing PEC in Malaysia.

Materials and Methods: In-depth interview using semi-structured open-ended questions were designed to explore the challenges of implementing PEC. Fifteen private optometrists across Malaysian were interviewed via purposive sampling until the data were saturated. The interviews were audio-recorded, transcribed and analysed.

Results: Four major themes emerged: working environment, support and recognition, self-sufficiency and customer influence. The first major theme identified a lack of time and equipment in the workplace as a barrier to PEC implementation. The second major theme acknowledges the lack of support and recognition for PEC practise from financial bodies, the government, Malaysian Optical Council (MOC) and other eye professionals. Meanwhile, some practising optometrists faced significant challenges due to their lack of self-sufficiency regarding skills, knowledge and confidence. The final major theme, customer influence, reflects the customer's role in shaping eye care delivery through their perception and acceptance of PEC.

Conclusion: Each of the issues identified played a significant impact in impeding PEC implementation in Malaysia. This study is the first step toward developing tailored interventions to improve eye care delivery in Malaysia.

KEYWORDS:
Primary eye care; scope of services; optometrists; challenge; qualitative research

INTRODUCTION

Primary eye care (PEC) is defined as the 'provision of appropriate, accessible, and affordable care that meets patients' eye care needs comprehensively and competently, which should be carried out by PEC practitioners'.[1] It is a frontline activity and an essential component of eye care, aiming not only to prevent blindness and visual impairment but also to provide treatments that reduce ocular morbidity.[21,22] In most parts of the developing world, PEC is provided by primary health care (PHC) workers; in developed countries, it is professionals such as optometrists who provide PEC.[18,19] Optometrists can provide a wide range of PEC services, including refraction, prescription of optical aids and detection of eye disease through binocular vision testing, fundoscopy, slit lamp examination, tonometry and visual field testing.[18] Nonetheless, the scope of optometric practise varies greatly around the world.[18] It ranges from optical technology and visual function services in Japan, to additional ocular diagnostic services in Indonesia and Hong Kong[25], to ocular therapeutic services in New Zealand[26], possibly due to differences in health systems and optometric recognition.[13,18]

In Malaysia, the eye care provisions are catered by public healthcare and private services. Ideally, the flow of eye care services in public healthcare starts with PEC service by the health clinics, secondary care service by the district hospitals, to tertiary care service by the tertiary hospitals. However, most clinics in the public sector could not cater to the demands for PEC services due to the limited availability of optometrists and limited access to essential ophthalmic instruments.[2,20] This situation has led to the increasing workload of the eye clinic at tertiary centres where most PEC is catered.[5,20] This, in turn, cause long waiting appointment list, delay in the provision of appropriate care and indirectly reduce the quality of eye care in Malaysia.[2,15]

The Malaysian National Eye Survey (NES) I and II demonstrated that blindness and visual impairment rates in Malaysia predominantly contributed to avoidable eye diseases.[3,4] In NES I, uncorrected refractive errors was the leading cause of visual impairment (48%), followed by cataract (39%) and retinal diseases (24%). In contrast, cataract was the leading cause of blindness (58.6%), followed by diabetic retinopathy (10.4%) and glaucoma (6.6%) in NES II.[4] Furthermore, 86.3% of the cause of blindness were avoidable in NES II.[3] The findings suggested an urgent need to assess the current provision of PEC services and the barriers to the utilisation of eye care in this country. In addition, optometrists in the private sector should shoulder some of the responsibility of reducing ocular morbidity by offering PEC services in their practise.[2]

This article was accepted: 16 May 2023
Corresponding Author: Nurul Ain Yahaya
Email: nurulainyahaya@iium.edu.my

Several studies have been conducted to assess the practise of optometrists in Malaysia's private sector.[5,6] The findings highlighted that the scope of practise is still limited to refractive examination and dispensaries in most practises.[5,6] However, none of the studies focuses on the underlying causes of poor implementation of PEC, which are the challenges. This study, therefore, explored the present challenges of PEC implementation by gathering perspectives from optometrists in the private sector. It is hoped that the study's findings will be used to develop tailored interventions to improve eye care delivery in Malaysia.

MATERIALS AND METHODS

The study was a qualitative design using IDI. Fifteen registered optometrists with at least a year of working experience in the private optometry practise within Peninsular Malaysia were selected as respondents using purposive and snowball sampling. Those practising in hospitals, LASIK centres and academic institutions were excluded from the study. The interview guide was developed, pre-tested and piloted on two subjects to ensure the instrument's validity.[7] Subsequent editing was made based on the pre-testing and pilot study feedback.

The semi-structured IDI was conducted at the respondents workplace from September to December 2019. With written consent from every respondent, all interviews were audio-recorded. Interviews were either in Malay or English, depending on the respondent's preference. The duration of the interview ranged from 30 minutes to 120 minutes. Prompts and probes were used to elicit in-depth responses whenever appropriate. The IDI recordings were transcribed verbatim and analysed using a thematic analysis framework.[8]

The thematic analysis approach involved data familiarisation, generating initial codes, searching, reviewing and defining the themes.[8] The identified themes across the analysed transcripts were merged, classified and constructed into themes and subthemes. The relevant quotes codes were produced to represent the final themes. The verbatim transcription, analysis and identification of themes were made in the Malay language using NViVo software version 12.0. Only the excerpt of the interviews was translated into the English language with the agreement of the research team. The study's trustworthiness was obtained by adhering to the trustworthiness criteria.[9] The ethical approval was obtained from IIUM Research Ethics Committee (IREC) with ID number 153/20.

RESULTS

The optometrists' working experiences ranged from 3 to 26 years (mean: 12.87 years). Table I illustrates a summary of the respondents' demographic information.

This study identified four significant challenges of implementing PEC in the private practise: working environment, support and recognition, self-sufficiency and customer influence. The themes and subthemes of the obstacles to implementing PEC among optometrists in the private sector in Malaysia are depicted in Figure 1.

Theme 1: Working Environment

Based on interviews with respondents, we identified the workplace environment as one of the challenge to practising PEC. Time constraints and lack of equipment emerged as two subthemes under the workplace environment.

Subtheme 1: Time constraint

Most respondents agreed that PEC requires more time than basic eye examination. Mrs. H, who previously worked in practises that did not implement PEC, commented on how the PEC routine at her current practise significantly lengthened the examination procedure.

"The second challenge is time. From my experience, I spent about 5-10 minutes completing eye examinations in my previous workplace. But now, I need to spend 20- 45 minutes per customer to complete an eye examination".
(Interview 05: Mrs. H)

Subtheme 2: Lack of equipment

All respondents stated a lack of facilities is a barrier to implementing PEC. It includes a lack of instrumentation to practise PEC.

"The second barrier to implementing PEC in practice is the instrumentation. I am quite fortunate because my practice is equipped with auto-K and slit lamps. But that is not the case for other optometrists."
(Interview 01: Mr. M)

Theme 2: Support and Recognition

Support and recognition are also important factors in implementing PEC in private practise. It is difficult for optometrists to broaden their scope of services without strong support from governing authorities. There are four subthemes under support and recognition: financial bodies, government, MOC and other eye care professionals.

Subtheme 1: Financial Bodies

PEC implementation incurs high costs owing to the installation and maintenance of ophthalmic instrumentation, such as slit-lamp biomicroscopy (SLB), fundus camera and tonometer. However, there is lack of support received from the financial bodies to implement PEC.

"I have repetitively gone to the bank and related agencies; It is difficult to secure the loans because I am not a public worker. It will easily be rejected if I want to secure a loan to open my practice through the bank. So I need to provide my capital".
(Interview 08, Mrs. E)

Subtheme 2: Government

The government's support and recognition are critical for optometrists to function appropriately in a country. According to Mr. R, this is not the case in Malaysia, where support for the optometrist profession is still lacking.

"The last challenge would be from the government…. The government focused more on mortality and morbidity, but

Table I: Demographic information of the respondents

Name	Age	Gender	Experience (year)	Workplace Location	Ownership
Interview 01, Mr. M	41	M	19	Mall, Pahang	Staff
Interview 02, Miss Y	31	F	7	Shop lot, Pahang	Staff
Interview 03, Mr. R	33	M	10	Shop lot, Selangor	Owner
Interview 04, Miss R	28	F	4	Shop lot, Perak	Owner
Interview 05, Mrs. H	34	F	10	Shop lot, Perak	Owner
Interview 06, Mr. E	39	M	16	Shop lot, Pahang	Owner
Interview 07, Mr. J	51	M	26	Shop lot, Terengganu	Owner
Interview 08, Mrs. E	35	F	8	Shop lot, Terengganu	Owner
Interview 09, Mr. C	54	M	30	Shop lot, Malacca	Owner
Interview 10, Mrs. S	31	F	7	Shop lot, Malacca	Owner
Interview 11, Miss B	27	F	4	Shop lot, Selangor	Staff
Interview 12, Mr. A	34	M	3	Shop lot, Selangor	Owner
Interview 13, Mr. D	34	M	10	Mall, Kuala Lumpur	Staff
Interview 14, Mr. K	36	M	13	Shop lot, Kedah	Staff
Interview 15, Mr. N	51	M	26	Shop lot, Pulau Pinang	Owner

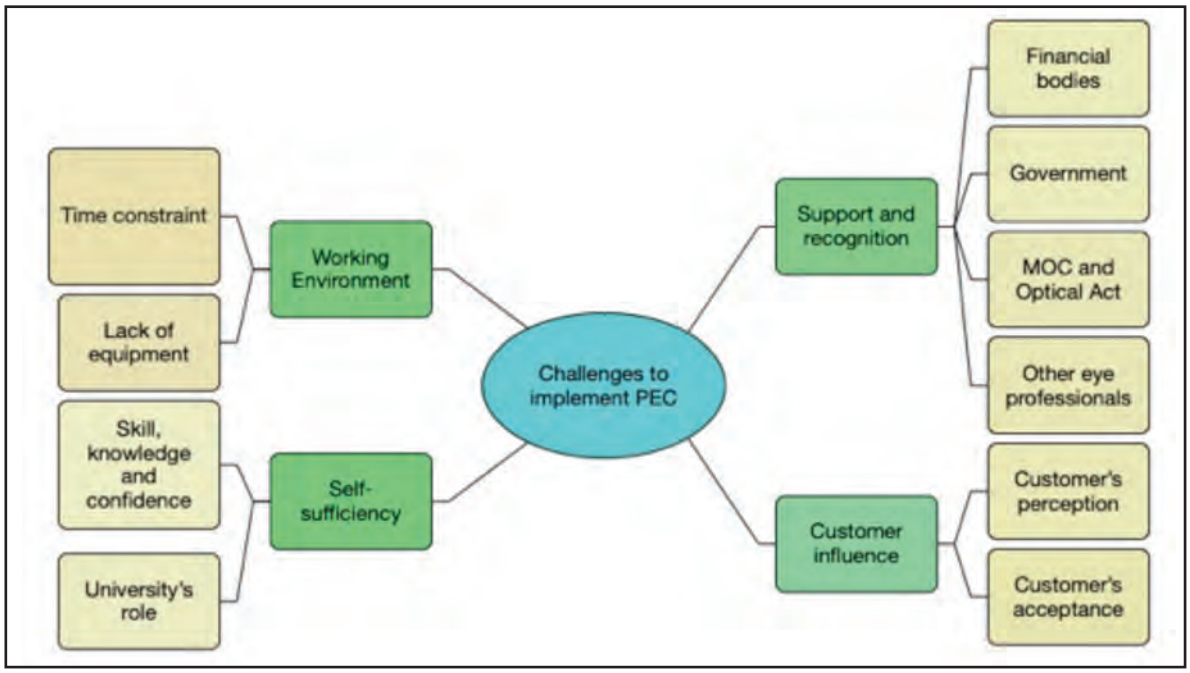

Fig. 1: The themes and subthemes of the challenges to implementing PEC among optometrists in the private sector in Malaysia

ignores the visual impairment. The current government does not support our industry".
(Interview 03, Mr. R)

Subtheme 3: Malaysian Optical Council and Optical Act
The optometrist and optician profession in Malaysia is regulated by law under Act 469, also known as Optical Act 1991. Meanwhile, the MOC is responsible for monitoring optometrists' service and practise under this act. The interviews revealed several issues with the MOC and the Optical Act 1991, including an outdated act and a lack of enforcement.

"I would like to see the new optical act be gazette and enforced. The weak current optical act currently limits our practice."
(Interview 07, Mr. J)

Subtheme 4: Other Eye Care Professionals
Collaboration between eye care professionals like ophthalmologists is critical for effective PEC delivery in a country. However, some respondents expressed dissatisfaction with the lack of recognition from other Malaysian eye care professionals.

"Even the doctor does not recognise the capability of an optometrist. From my experiences, I had a few doctors as my customers. They said, 'Ohh.. u can practice up to this level?'"
(Interview 02, Miss Y)

Theme 3: Self-sufficiency
Self-sufficiency was the third major theme for the challenges of implementing PEC among optometrists in Malaysia's private sector. It has two subthemes: skill, knowledge,

confidence and the university's role.

Subtheme 1: Skill, Knowledge and Confidence
Delivering PEC to the community requires competent optometrists in knowledge and skills. However, keeping up with knowledge and skills on the recent technologies in diagnosing and managing ocular ailments is undoubtedly a real struggle.

"The second challenges were knowledge. For example, I graduated 30 years ago, so I know from that time. That is why I founded # (mentioned an organisation), as I've said, for continuous education. It is because our profession is dynamic, with many new findings.
(Interview 05, Mr. J)

Confidence is essential in fostering a competent optometrist, which can be honed through experience. However, due to the current practise in some retailers that focusses on refractive examination, some optometrists are losing the opportunity to practise PEC thus affecting confidence.

"I think the first challenge would be myself. I have abandoned the PEC practise for quite some time, so the decision to practice back PEC was the most difficult thing to do. I haven't practised PEC for two years, so I feel nervous when performing a retinoscopy. I don't know whether I did it right."
(Interview 10, Mrs. S)

Subtheme 2: University Role
The optometrist is a credible and accredited profession obtained through undergraduate training. The university plays a vital role in optometrists' self-adequacy to practise PEC in their professional lives.

"I think the university should introduce a course or topic on PEC in the private sector. Then invite an industry veteran to speak to the graduates to inspire them to practise PEC in the future."
(Interview 10, Mrs. S)

Theme 4: Customer Influence
The last theme for the challenges to implementing PEC was customer influence. Some optometrists feel that the customer's perception and acceptance affected their motivation to practice PEC.

Subtheme 1: Customer's perception

"There are some customers who perceived us as regular salesperson. They do not recognise our roles as an optometrist."
(Interview 11, Miss B)

Subtheme 2: Customer's acceptance

"They are hesitant to receive PEC and unwilling to spend extra time in our practice."
(Interview 01, Mr. M)

DISCUSSION

This qualitative study addressed the main challenges of implementing PEC among optometrists in private sectors in Malaysia. The four major themes identified were the working environment, lack of support and recognition, self-sufficiency and customer influence. The diversity of these practise factors demonstrates the complexities of eye care delivery across the country.

This study has shown that the workplace environment is one of the barriers to the practise of PEC. The subthemes were time constraints and lack of equipment. These findings are consistent with those in the literature where lack of equipment and time factors are the major challenges.[10] Due to the time-consuming nature of PEC, our respondents admitted that they generally lack time to conduct clinical testing and consultations. This in turn influenced the customer' desire to receive PEC. The second subtheme within the working environment was the lack of essential ophthalmic equipment such as SLB, auto keratometer (Auto-K), fundus camera, tonometer and visual field analyser. All of these equipment are valuable in the prescription of contact lenses and the detection of ocular disorders such as diabetic retinopathy and glaucoma, which are included in PEC services. The lack of equipment is directly attributable to the high cost associated with implementing PEC. Interviews with practise owners revealed that they experienced financial difficulties in setting up PEC. One optometrist said, *"I am from an intermediate economic background, not rich people with access to funding. So, when I want to open optometry practice with PEC, I need to consider how to buy instrumentation"*. In addition, optometrists working in a chain store also noted a shortage of instruments, which is consistent with the previous finding.[5,6] Although it is not their responsibility to provide the equipment, some claim that their company has not yet invested in PEC. A typical optical chain store in Malaysia focuses mainly on refractive and dispensary services rather than PEC.[6] Thus, the challenge in the workplace is very closely related to the support from the optical company itself.

The second theme, perhaps the most intriguing, was the lack of support and recognition from the financial bodies, government, MOC and the Optical Act and other eye care professionals. The first subtheme of lack of support from financial institutions is related to the high cost of setting up PEC and the financial difficulties mentioned earlier. The difficulty highlighted by the business owners in setting up PEC may have dampened motivation to upgrade their practise. It is suggested that the authority take further measures to provide financial support in order to have a better chance of obtaining the loans. On the other hand, it is interesting to note that there is still a lack of support from the government. Referring to Mr. R's comment in the Results section, he opined that the government ignores visual impairment and does not support optometrists. While this comment may seem biased, it has some truth to it, as the assumption of reality (ontology) in a qualitative study is subjective and multi-faceted, as noted by the participants in the study.[23] Nevertheless, the government has paid attention to visual impairment as seen in some programmes such as Klinik Katarak Kementerian Kesihatan Malaysia (KK-KKM) and Amblyopia and Low Vision Screening (AVIS).[20] However,

the measures taken by the government are limited due to concerns about the financial stability of the health system.[24] Meanwhile, the lack of recognition of optometrists in the private sector by the government and health professionals has been noted. Optometrists have been around in Malaysia for about 30 years.[20] Despite this, the optometry profession is still not sufficiently recognised, making it difficult to expand services. Recently, during the COVID-19 pandemic, it was evidenced that optometry was not initially recognised as an essential service and was excluded from providing services during the Movement Control Order (MCO).[11] It was suggested that the situation was exacerbated in part by government misconceptions about the premises of opticians and optometrists. The role of optometrists as PEC practitioners and their ability to diagnose and treat eye diseases were not sufficiently recognised. Finally, there was also a lack of support from the Optical Act 1991.[12] MOC, which regulates eye care professionals, including optometrists in Malaysia, has proposed a new Optometry Act to address the shortcomings of the current act's shortcomings. However, it will be a long time before the new act is finally tabled in the Malaysian Parliament.

The third challenge faced by the optometrist in private practise was self-sufficiency. The first subtheme of self-sufficiency was skills, knowledge and confidence and the second subtheme was the role of the institution in supporting the development of self-sufficiency. Self-sufficiency of optometrists is important to provide impeccable PEC services to the public. Under normal circumstances, graduates from local universities are equipped with enough knowledge, skills and confidence to practise PEC. This is partly due to the universities strict adherence to the Malaysian Qualification Agency (MQA) guidelines to obtain accreditation and ensure that the graduates are competent and on par with other optometrists worldwide. However, when optometrists started working, many of them were employed by companies that do not apply PEC in their workplace. This might leads to a loss of skills and confidence in performing PEC, as Mrs. S describes in the Results section. Our finding is consistent with the study from Singapore, where optometrists' confidence in screening and co-management of common eye diseases such as cataract, diabetic retinopathy, glaucoma and age-related macular degeneration was generally low.[13] The respondents in this study used many ways to overcome these challenges: developing peer support systems, attending seminars or conferences and referring to textbooks. In addition, MOC through the Ministry of Health (MOH) has introduced a Continuing Professional Development programme (CPD) for optometrists and opticians to gain knowledge, skills and experience using myCPD2 system.[14,16] This is a practical solution to the obstacles faced by our optometrists in the private sector. However, we recommend that seminars or conferences be based on practicality and the real needs of the industry. On the other hand, higher institutions could help shape the mindset of our future optometrists by emphasising the importance of PEC in the curriculum.

The final challenge noted by our respondents was customer influence, with subthemes of customer perception and acceptance. While customers are not an immediate barrier to PEC adoption, several of our respondents expressed that they feel demotivated if they are not recognised as optometrists. This event demonstrated that the public's understanding of the role of optometrists could still be increased as there is still some misunderstanding about the profession in Malaysia. In addition, it is worth noting that the scope of practise of optometrists in Malaysia is still limited.[5,6] Meanwhile, the public's acceptance of optometrists who already offer PEC is not always favourable. Usually, customers come to the optometrist to get spectacles made, which only requires a refractive examination that can be completed in about 10 minutes. However, in a practise that offers PEC, the duration of the eye examination can extend up to 30 minutes to perform more extensive examinations such as SLB, fundus camera and tonometer. Several optometrists agreed that some consumers were unwilling to pay an additional fee for diagnostic examinations. This finding is consistent with a systematic review study on the facilitators and barriers for optometrists in providing eye care, which cited patient disinterest and low affordability as barriers.[10] Despite the challenges, the optometrists in our study displayed perseverance to resolve the situation. They worked tirelessly to raise public awareness of the importance of PEC through direct consultation, community services and the use of social media platforms. It is envisioned that the resilience of these optometrists will be shared by all optometrists in Malaysia to promote public awareness of PEC.

The study's first and second major challenges were unfortunately sit outside optometrists' loci of control, requiring organisational level system change. Compared to hospital-based eye care, optometrists in private practise need multiple levels of management and leadership influence to accomplish change.[10] This can make addressing organisational level barriers in eye care particularly challenging. However, for the initial barrier of working environment, when the practise of PEC is limited, notably by the company, it is suggested that a new optometry graduate explore more possibilities in terms of employment. It is noted that the second theme is more challenging as it involves external parties. The Association of Malaysian Optometrists (AMO), a non-governmental organisation (NGO) representing optometrists in Malaysia, has made significant efforts to defend our profession's standing, particularly before the government.[11] Therefore, individuals practising optometry should join the effort to gain recognition for the optometry profession by adhering to the World Council of Optometrists (WCO) standard scope of practise.[18] Regardless of the lack of specialised equipment, basic optometric tools such as retinoscopy and ophthalmoscopy can be used to commence PEC practise. Lastly, it is hoped that drafting the new optometry act could be expedited for the better future of Malaysian eye care.

The barriers identified and analysed in this study were broad, encompassing concerns at both the optometrist and organisational levels. This study's findings revealed the complexities of PEC in Malaysia and provided a general grasp of the underlying obstacles. However, the limitation of this study is inherent to all qualitatively designed studies, specifically, its limited representation of optometrists in the private sector in Malaysia. Therefore, our future work involves the development of a quantitative survey using our findings to tackle the problem.

CONCLUSION

In conclusion, our study explored the challenges perceived by the optometrists in private sector Malaysia in implementing PEC. The challenges perceived were significant as they may play a role in impeding PEC implementation. This study is the first step toward developing tailored interventions to improve eye care delivery in Malaysia.

ACKNOWLEDGEMENTS

The authors would like to thank lecturers in the Kulliyyah of Allied Health Sciences and Kulliyyah of Medicine IIUM for their advice in data collection and analysis. On the other hand, the contribution of the private practise optometrists throughout Peninsular Malaysia to participate in this study is also highly appreciated. This study was fully self-supported by all the contributing authors.

CONFLICT OF INTEREST

There is no conflict of interest related to this study.

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APPENDIX

BACKGROUNDS	
To begin this interview, I'd like to ask some questions about you and your workplace as an optometrist	
QUESTIONS	**PROMPTS/ PROBES**
1. How long have you been practicing as an optometrist?	
2. Can you tell me a bit on your workplace and your position there?	• Type of practise • Type of customers • Responsibility at the workplace
3. So you are working in _____, if let say a customer enter your practice, What is the standard of the workflow to serve the customer from beginning till the end?	• Do you practice primary eye care (PEC)?
PRIMARY EYE CARE & CHALLENGES	
Thank you for your responses. I'd like to now ask you more detail questions regarding PEC and it's challenges.	
QUESTIONS	**PROMPTS/ PROBES**
4. Could you please describe PEC in your own words?	
5. PEC might seem a simple 'phrase' but definitely a huge task from all eye care provider. It might looks excellent and idealistic in paper, but in reality it is indeed difficult to be executed. What is your opinion on the implementation of PEC in the retails sector, Malaysia?	• Do you think it can be successfully implemented? o Give your reason.
6. If PEC to be executed in your practise, what seems to be the biggest challenge you will face? (To be asked if PEC is not yet executed in the practice)	• Why do you think it is the biggest challenges? • What should be done to overcome it?
7. Since you implement PEC in your practice, what is the biggest challenges did you faced? (To be asked if PEC not yet executed in the practice)	• Why do you think it is the biggest challenges? • What should be done to overcome it?
8. Are there any other challenges that you think significant?	• What should be done to overcome it?
OPINION TO IMPROVE PEC	
Thank you for your responses. I'd like to now ask you more detail questions regarding PEC and it's challenges.	
QUESTIONS	**PROMPTS/ PROBES**
9. What do you think could motivates you as an optometrist to implement primary eye-care?	•
10. Imagine you are a very important person in AMO or MOC, and you have direct contact with current minister of health, what would you like to suggest the minister to support PEC expansion of private practices over a coffee break?	•

We are now reaching the end of our discussion. Before we end, do you have any questions or do you want to add more opinions regarding our discussion?
Thank you so much for your valuable answers and opinion It is so much pleasure to meet you and discuss this matter. If there is any matter arise, you can contact me via_____? Is that okay if I contact you after the interview if I need further clarification?

ORIGINAL ARTICLE

Fungus isolated from dermatomycoses: a 9-month prospective study at Hospital Melaka

Lim Chui Ng, MBBS, MRCP[1], Choon Sian Lee, MD, MRCP, AdvMDerm[1], Bee Bee Lim, MD, MPath[2], Ratna Mohd Tap, BSc, MSc[3], Xue Ting Tan, PhD[3], Min Moon Tang, MD, MRCP, AdvMDerm[4]

[1]Department of Dermatology, Hospital Melaka, Malaysia, [2]Department of Pathology, Hospital Melaka, Malaysia, [3]Institute of Medical Research, Malaysia, [4]Department of Dermatology, Hospital Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Dermatomycoses are common superficial cutaneous fungal infections which affect the skin, nails and human hairs. It affects 20 to 25% of the world population. The causative fungus varies geographically across the globe. Study on dermatomycoses is crucial to identify the aetiological fungus involved locally. The study aimed to determine the causative fungus of superficial fungal infections of the skin, nail and hair in patients presented to Hospital Melaka.

Methods: This was a prospective study conducted from 15th January 2022 till 15th October 2022 at Dermatology Clinic, Hospital Melaka. Subjects with clinical dermatomycoses were included in this study. The samples were collected from skin, nails and hairs clinically affected by tinea corporis/cruris/pedis, onychomycosis and tinea capitis respectively. A potassium hydroxide (KOH) study was performed on the sample in which the fungal hyphae/yeast positive subjects were sent for fungal culture and fungal PCR test.

Result: A total of 222 clinical samples from skin, nails and hairs with a clinical suspicion of dermatomycoses yielded fungal hyphae/yeast in KOH. Majority of the samples were collected from skin (138, 62.2%), followed by nails (65, 29.3%) and hairs (19, 8.6%). Male to female ratio was 1.18: 1. The age ranged from 2 to 87 with the median of 55.5-years-old. Out of 222 samples, 150 (67.6%) were fungal culture positive. From fungal culture positive samples, 87 samples were from tinea corporis, 50 samples were from onychomycoses and 13 samples were from tinea capitis. *Trichophyton rubrum* (39, 44.8%) was the commonest dermatophyte isolated in tinea corporis/cruris/pedis. Non-dermatophyte moulds (NDM, 35, 70%) were the main fungi isolated in onychomycosis. *Microsporum canis* (7/53.8%) was the principal causative fungus among patients with tinea capitis. Among 150 fungal culture positive samples, 76 were fungal PCR positive. Only 38 samples consistently isolated same fungal species in both fungal culture and PCR test.

Conclusion: Majority of tinea corporis and tinea capitis fungal culture isolated dermatophytes, especially *Trichophyton rubrum* and *Microsporum canis*, respectively. Non-dermatophyte moulds were mainly isolated in onychomycosis.

KEYWORDS:
Dermatomycosis, dermatophytes, moulds, Trichophyton rubrum, Microsporum canis

INTRODUCTION

Dermatomycoses are superficial cutaneous fungal infection which affects the skin, nails and hairs of humans. It is caused by dermatophytes, non-dermatophyte moulds (NDM) and yeasts. Dermatophytes consist of *Trichophyton, Microsporum* and *Epidermophyton*. Non-dermatophyte moulds include other filamentous fungi such as *Fusarium* and *Aspergillus*. Yeasts which are round or oval, encompass *Candida, Malasezzia* and *Trichosporon*.

Superficial skin mycosis is a common skin infection that affects 20–25% of the world population.[1] Transmission of dermatomycoses can occur by direct contact with infected people, animals and contaminated soil.[2] The causative fungus varies due to the difference in regions, climate, lifestyles, ages and the affected sites.[3] Dermatophyte was the commonest fungus isolated in United State[4] China[5] and Vietnam.[6] Non-dermatophyte moulds were commonly identified in Malaysia population affected by onychomycosis.[7,8]

To date, the number of studies or audits on the causative agents of dermatomycoses in Malaysia is limited. In addition, they are subjected to bias due to the retrospective nature of the studies. Here we aim to investigate the common pathogenic fungi involved dermatomycoses in our local population.

MATERIALS AND METHODS

This was a prospective study conducted from 15th January 2022 till 15th October 2022 at Dermatology Clinic, Hospital Melaka. We included all patients with clinical dermatomycoses and were treatment naïve. We excluded patients who had already received anti-fungal drugs in the last 6 months. Clinical samples included skin scrapings, hair plucking and nail clippings of the respective diseased sites. After obtaining proper informed consent, skin scrapings were collected from tinea corporis/cruris/pedis; nail clippings from onychomycoses; plucked hairs from tinea capitis.

This article was accepted: 17 May 2023
Corresponding Author: Ng Lim Chui
Email: ngsteve88@yahoo.com

The sites of lesions were cleaned with 70% alcohol. The skin scrapings were collected from the active edges of the lesion with a sterile blunt scalpel. The infected nails were clipped with nail clipper. The affected hairs were epilated from the scalp lesion with sterile forceps. All samples were subjected to direct microscopic examination with 10 to 20% potassium hydroxide (KOH) solution. Sample which yielded positive fungal bodies (yeasts and hyphae) will then be seeded on the surface of Sabourouds dextrose agar media from Thermo Fisher Scientific, incubated at 30ºC and culture growth was analysed daily. The isolated fungi were identified based on the examination of the cultural characteristics and microscopic morphology. Cultures without growth during a period of up to 4 weeks were considered negative.

Polymerase chain reaction (PCR) was performed for positive dermatophytes' cultures for comparison study. Using bead bashing method of Fungal/Bacterial DNA MiniPrepTM kit (Zymo Research, USA), the fungal DNA was extracted according to the manufacturer instructions. Thereafter, DNAs were amplified by PCR using a set of universal primers; a forward primer (ITS1: 5′- TCCGTAGGTGAACCTGCGG-3′) and a reverse primer (ITS4: 5′-TCCTCCGCTTATTGATATGC-3′). The use of primers ITS1 and ITS4 have been verified in numerous dermatophyte studies to screen for the presence of fungus in the specimens.9,10 The PCR amplification was done using a Thermal Cycler (Gene Amp, PCR system 9700, Applied Biosystems, USA) in a total volume of 25 µl consisting of 3.0 µl DNA, 12.5 µl MyTaq HS mix (Bioline Meridine Bioscience, London, UK), 0.5 µl of each primer and 8.5 µl of nuclease free distilled water. Quality control DNA were included in the assay. Amplified PCR fragments were analysed to determine DNA bands through which observed by UV transilluminator alongside DNA Ladder (100 bp). The amplified DNA was sent for sequenced by Apical Scientific Sdn Bhd and further analysed to identify the fungal species. Data was presented in table and further analysed using SPSS. Categorical data will be analysed using Chi square(crosstabs) to acquire "*p*" value. Demographic information and fungi isolated were summarised using descriptive statistics.

RESULTS

A total of 222 clinical samples of skin scrapings, nail clippings and hair plucking that showed hyphae or yeasts in KOH staining (KOH+) were included for final analysis (Figure 1). Majority of samples were collected from skin (138/62.2%), followed by nail (65/ 29.3%) and hair (19/ 8.6%). Out of 222 KOH+ samples, 150 (67.6%) had a positive fungal culture. Interestingly, of the 150 fungal culture positive samples, only 76 (50.7%) were fungal PCR positive. Only 38 (50%) samples had same fungal species identified in both fungal culture and PCR test. In another 38 (50%) samples, discordant fungal species was observed between PCR and culture.

As shown in Table I, the male to female ratio was 1.18: 1. The age ranged from 2 to 87 with the median 55.5-years-old. Majority were adults (108/48.6%). The median duration for onset of symptoms before presenting to our clinic was 5.5 months. Patients with weaken immune system such as those with diabetes mellitus, end stage renal failure (ESRF), human immunodeficiency virus (HIV) infection, nephrotic syndrome, malignancy, systemic lupus erythematosus (SLE) and those taking immunosuppressive agents (methotrexate, cyclosporin) yielded a significantly higher rate of *Trichophyton rubrum* compared to patients with normal immune system.

Based on fungal culture positive samples, 87 samples were from tinea corporis/cruris/pedis, 50 samples were from onychomycoses and 13 samples were from tinea capitis. The results were shown in Table II. Dermatophyte, especially Trichophyton rubrum was the most common fungus isolated in tinea corporis. Non-dermatophyte moulds were the main fungi isolated in onychomycosis, in which *Aspergillus species* being the most common species isolated. *Micosporum canis* was the principal causative fungus among patients with tinea capitis. Results were shown in Table III.

Based on the fungal PCR positive result, there was a total of 42 samples from tinea corporis/cruris/pedis, 25 samples from onychomycoses and nine samples were from tinea capitis as shown in Table II. Table III illustrated the fungal species resulted in the superficial fungal infections. *Trichophyton rubrum* was the most common fungus found in PCR result for tinea corporis/cruris/pedis and onychomysosis. While *Microsporum canis* was the most common fungal isolated in tinea capitis. Among 38 concordant fungal culture and PCR result (same fungal species identified in both fungal culture and PCR), dermatophyte *Trichophyton rubrum* was the most common species identified (18, 47.4%) followed by *Trichosporon mentagrophytes* (6,15.8%).

DISCUSSION

Tinea infection (dermatophytosis) are superficial fungal infections caused by dermatophytes that affect skin, nails and hairs. It is a filamentous fungus that invades cutaneous keratinised stratum corneum e. g. skin, hairs and nails. The pathogenesis for dermatophytosis starts with interaction of dermatophyte with host cell, resulting in adhesion to epidermal layer within 1 hour. This process is mediated by adhesins protein present on the fungal cell wall.[11] This is followed by penetration of stratum corneum by secreting keratinolytic proteases, serine subtilisin and fungalysin. Then arthroconidia germinate and the hyphae inoculate through stratum corneum to prevent removal with cell shedding. This happens within 3 to 4 hours. Within 1 to 3 days, the hyphae will spread through over the skin.[11] In the fungal cell wall, there is a glycoprotein-mannan which promotes fungal infection by inhibiting proliferation of keratinocyte. This protein prevents shedding and suppresses inflammatory response. Cell mediated immune response is greatly suppressed by mannans from various species of dermatophytes. For instance, *Trichophyton rubrum* produces more mannan than *Microsporum canis*. Hence, *Trichophyton rubrum* can suppress lymphoproliferation more effectively as compared to *Microsporum canis*. This has contributed to the less inflammation and more chronicity in *Trichophyton rubrum* infection compared to *Microsporum canis*.[11] This probably explained *Trichophyton rubrum* being the most common causative fungus among tinea corporis/cruris/pedis patients in our population.

Table I: Clinical characteristics of patients with clinical suspicious of dermatomycosis

Characteristics			Total (n = 222)	Culture positive n = 150			Culture negative n = 72			*p* value
				skin	hair	nail	skin	hair	nail	
Age in years	Median		55.5							
	Age range	Paediatric (<10):	14	0	12	0	0	2	0	0.016
		Adolescent (1 to 19)	13	4	0	0	6	3	0	
		Adult (20 to 60)	108	59	1	14	27	1	6	
		Elderly (>60):	87	24	0	36	18	0	9	
Gender		Ratio (male:female)			1.18:1					0.981
		Male	120	43	11	27	29	2	8	
		Female	102	44	2	23	22	4	7	
Ethinicty		Malay	163	71	12	29	38	6	7	0.845
		Chinese	45	12	1	15	10	0	7	
		Indian	11	3	0	5	2	0	1	
		others	3	1	0	1	1	0	0	
Occupation		Blue Collar	49	23	0	13	9	1	3	0.181
		White collar	29	12	0	5	7	5	0	
		Retired personnel	18	7	0	5	5	0	1	
		Unemployed	62	18	2	25	12	0	5	
		Student	32	5	11	0	13	0	3	
		housewife	32	17	0	7	5	0	3	
Risk factor For fungal infection		Low immune status*	75	29	1	29	13	0	3	0.015
		No risk of low immune	147	58	12	21	38	6	12	
Animal or plant contact		Animal contact	67	21	8	13	18	3	4	0.463
		Plant contact	30	11	0	10	7	0	2	
		No contact	125	55	5	27	26	3	9	

* Low immune status included those with underlying diabetes mellitus, ESRF, HIV, nephrotic syndrome, malignancy, SLE and those taking immunosuppressive agents.

Table II: Types of fungal isolated from culture or polymerase chain reaction based on sample collected site

Type of test / Type of test	Fungal culture				Fungal PCR			
	Skin	Hair	Nail	Total	Skin	Hair	nail	Total
Dermatophyte	49(56.3)	10(76.9)	1(2)	60	35(83.3)	8(88.9)	7(28)	49
Non-dermatophyte moulds	24(27.6)	3(23.1)	41(82)	67	1(2.3)	1(11.1)	7(28)	14
Yeast	14(16.1)	0	8(16)	23	6(14.3)	0	11(44)	13
Total	87	13	50	150	42	9	25	76

Table III: Fungus isolated from fungal culture or polymerase chain reaction

Fungus isolated from fungal culture/PCR	Tinea corporis/cruris/ pedis n (%)		Onychomycosis n (%)		Tinea capitis n (%)	
	Culture n = 87	PCR n = 42	Culture n = 50	PCR n = 25	Culture n = 13	PCR n = 9
Dermatophyte						
I. *Trichophyton rubrum*	39(44.8)	20(23)	1(2)	4(8)	2(15.4)	2(15.4)
II. *Trichophyton mentagrophytes*	7(8.0)	14(16.1)	0	2(4)	0	0
III. *Trichophyton tonsurans*	2(2.3)	0	0	0	0	0
IV. *Trichophyton species*	0	0	0	1(2)	0	0
V. *Microsporum canis*	0(0)	1(1.1)	0	0	7(53.8)	6(46.2)
VI. *Microsporum gypseum*	0(0)	0	0	0	1(7.7)	0
VII. *Epidermophyton*	1(1.1)	0	0	0	0	0
Yeast						
I. *Candida species*	13(14.9)	0	7(14)	0	0	0
II. *Candida albicans*	1(1.1)	2(2.3)	0	1(2.0)	0	0
III. *Candida orthopsilosis*	0	0	0	1(2.0)	0	0
IV. *Candida parapsilosis*	0	1(1.1)	0	1(2.0)	0	0
V. *Candida parapsilosis complex*	0	0	0	1(2.0)	0	0
VI. *Candida tropicalis*	0	1(1.1)	0	2(4.0)	0	0
VII. *Trichosporon*	0	1(1.1)	1(2)	2(4.0)	0	0
VIII. *Geotrichum*	0	0	1(2)	0	0	0
IX. *Apiotrichum montevideense*	0	0	0	1(2.0)	0	0
X. *Meyerozyma caribbica*	0	0	0	1(2.0)	0	0
XI. *Wickerhamiella shivajii*	0	0	0	1(2.0)	0	0
XII. *Saccharomyces cerevisiae*	0	1(1.1)	0	0	0	0
Non dermatophyte						
Hyalohyphomycetes						
I. *Aspergillus flavus*	0	0	3(6)	0	0	0
II. *Aspergillus fumigatus*	0	0	2(4)	0	0	0
III. *Aspergillus niger*	1(1.1)	0	7(14)	1(2)	0	0
IV. *Aspergillus terreus*	0	0	1(2)	0	0	0
V. *Aspergillus penicillioides*	0	0	0	0	0	1(7.7)
VI. *Fusarium species*	1(1.1)	0	10(20)	0	0	0
VII. *Fusarium keratoplasticum*	0	0	0	2(4)	0	0
VIII. *Fusarium solani complex*	0	1(1.1)	0	1(2)	0	0
IX. *Scopulariopsis species*	1(1.1)	0	0	0	0	0
X. *Penicillium species*	0	0	2(4)	0	0	0
Phaeohyphomycetes						
I. *Cladosporium*	8 (9.2)	0	1(2)	0	0	0
II. *Curvularia*	1(1.1)	0	3 (6)	0	0	0
III. *Exophiala*	2(2.3)	0	0	0	0	0
IV. *Phialophora species*	2(2.3)	0	0	0	0	0
V. *Scytalidium dimidiatum*	0	0	2(4)	1(2)	0	0
VI. *Hortea werneckii*	0	0	0	2(4)	0	0
Zygomycetes						
I. *Rhizopus*	0	0	4(8)	0	0	0
Non-sporulating hyaline mould	8(9.2)	0	5(10)	0	3(23.1)	0
Total	**87**	**42**	**50**	**25**	**13**	**9**

Interestingly, *Trichopyton tonsurans* was the predominant species described in United States[12] among patients with tinea corporis/cruris/pedis. In our study, we found that dermatophytes were mostly isolated from skin and hair samples. This is consistent with other studies in different countries such as New Zealand[13] and Mexico.[14] *Trichophyton rubrum* was the most frequent dermatophyte identified from skin samples for culture in China[5], French Guiana[15], and Brazil[16] (Table IV). M*icrosporum canis* was the most common fungus isolated from the scalp among the children with tinea capitis in this study. This finding was consistent with the studies among tinea capitis patients in Poland[17] and Northern Greece[18] (Table IV). Only one *Epidermophyton* isolated in the culture of skin sample.

Candida sp. was the most common yeast isolated from skin scrapings and nail clippings. This is consistent with other studies in most regions namely Africa[19], Australia[20], Europe[21] and Asia.[22] Candida is a dimorphic yeast that can exist in unicellular yeast form to filamentous hyphal form which can release hydrolytic enzymes including phospholipase, proteinase, lipase, esterase and haemolysing. These hydrolytic enzymes invade host cell through degradation of tissues cellular component and facilitate their adhesion, invasion, survival and dissemination.[23] Cutaneous candidiasis is characterised by erythematous patches with satellite lesions commonly found at warm, moist, creased areas such as the inframammary and groin skin. The most typical cause of diaper rash in young children is candida as

Table IV: Comparison dermatomycoses pattern in different countries

Author, year, country	n	Dermatophytes	NDM	Yeasts
Current study	150	*Trichophyton rubrum*: 42/60 (70%) *Trichophyton Mentagrophytes*: 7/60	*Fusarium sp*: 11/67 (16.4%)	*Candida sp*: 20/23 (71.5%)
Cai et al,[5] 2016, China	697	*Trichophyton rubrum*:392/588 *Trichophyton mentagrophyte*: 93/588 *Trichophyton violaceum*: 21/588	*Fusarium sp*: 4/5	*Candida albicans*: 54/104
Simonnet et al,[15] 2011, France	449	*Trichophyton rubrum*: 97/268 *Trichophyton mentagrophyte*: 38/268 *Microsporum canis*: 20/268	*Neoscytalidium dimidiatum*: 39/56	*Candida albicans*: 61/125
Silva-Rocha et al,[16] 2012, Brazil	113	*Trichophyton rubrum*: 21/59 *Trichophyton tonsurans*: 15/59 *Microsporum canis*: 8/59	*Fusarium sp*: 8/9	*Candida parapsilosis*: 18/45
Koussidou-Eremondi et al,[18] 2005, Northen Greece	611	*Microsporum canis*: 515/611 (tinea capitis 276/280) *Trichophyton rubrum*: 34/611 *Trichophyton mentagrophyte*: 11/611		*Candida albicans*: 20/611
Lange et al,[17] 2004, Poland	94	*Microsporum canis*: 58/94 (tinea capitis 25/30) *Trichophyton rubrum*: 16/94 *Trichophyton tonsurans*: 15/94		
Lim et al,[40] 1992, Singapore	87	*Trichophyton rubrum*: 17/27 *Trichophyton interdigitale*: 6/27 *Trichophyton mentagrophyte*:3/27 *Trichophyton violaceum*: 1/27	*Fusarium* : 7/13 *Aspergillus*: 3/13 *S. brevicaulis*: 1/13 *Aureobasidium*: 1/13 *Penicillium*: 1/13	*Candida albicans*: 45/47 *Candida parapsilosis*: 2/47

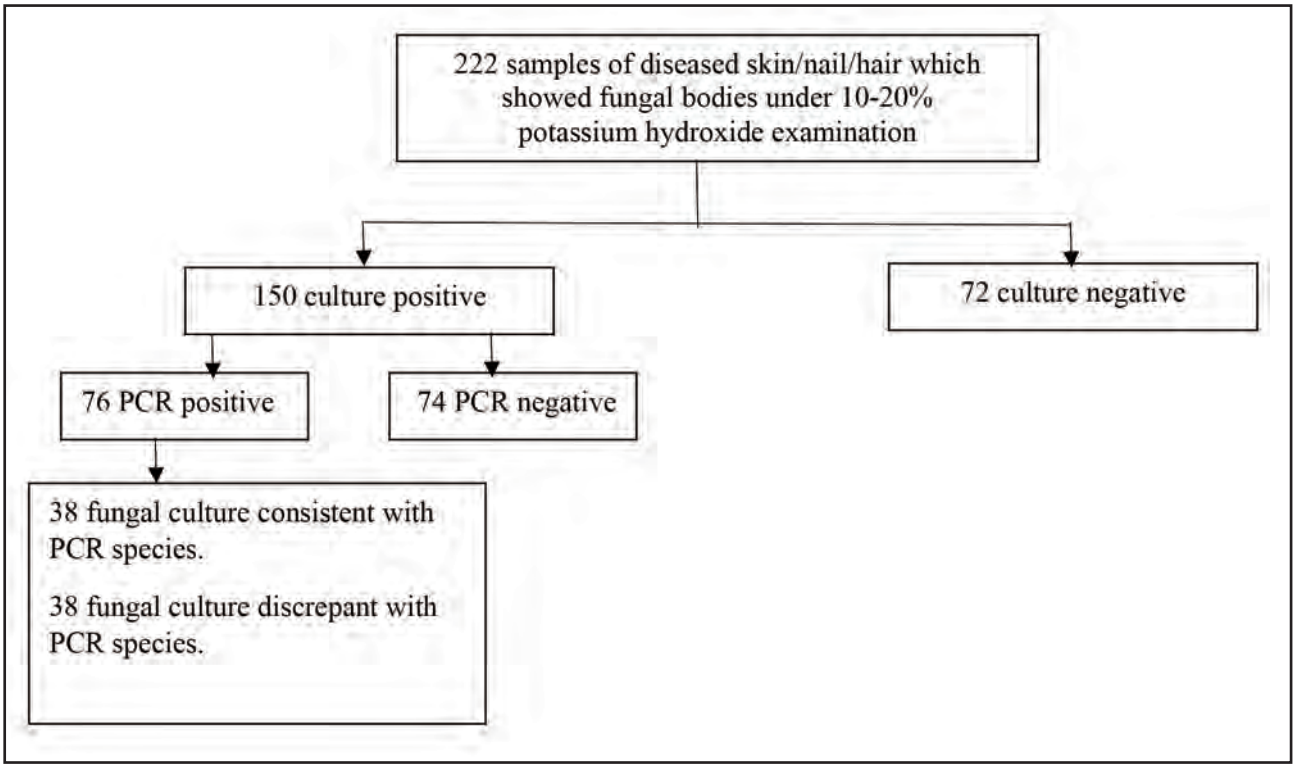

Fig. 1: The study workflow

diaper use provides a warm moist environment suitable for fungal growth. In addition, patients with low immune system e.g., diabetes, cancer, retroviral infection, use of broad-spectrum antibiotic, organ transplant are predisposed to candidiasis.

In onychomycosis, dermatophytes were the predominant fungi identified in Tunisia Afrika[24] and Turkey Middle East.[25] Moulds and dermatophytes were commonly found among onychomycosis patients in tropical country like Thailand.[26] Non dermatophyte moulds (*Hyalohyphomycetes*, *Phaeohyphomycetes* and *Zygomycetes*) were the most frequent fungi isolated among patients with onychomycosis in our study. This was consistent with other studies done in other states in Malaysia.[8,27]

As the spore of NDM can be ubiquitous in environment, therefore it may contaminate clinical specimen. Moulds isolated from nails were thought to be contaminants, however there are many studies observed that moulds could be pathogenic and are causative agents for onycomycosis.[28,29] It becomes pathogenic if it exhibits both positive microscopy and culture results or if a repeated culture yields the same isolated species.[30] Hence, the presence of mould in fungal culture result needs careful assessment and clinical correlation for its pathogenicity[7], especially in immunocompromised population. Non-sporulating hyphae are moulds that are unable to produce spores either due to unsuitable environment of it they have lost ability or need longer period to produce spores.[31] There are (16/10.7%) of non-sporulating hyphae in this study. In nature, fungi that don't sporulate in culture do produce spores. These fungi can result in irritant and allergy as well as systemic infections especially among population with impaired immune systems.[31] In addition, it is not possible to identify the precise non-sporulating hyphae unless sporulation can be induced, in which the process takes weeks to months.[31] Hence clinical judgment plays an important role in determining the clinical significance of non-sporulating hyphae.

In order to minimise false negative result, the technique to obtain good fungal nail samples is crucial. Micro-drilling, proximal sampling, and subungual curettage are the recommended methods to produce high culture yield for fungal nail culture as compared to conventional nail clipping.[32] Common practice of distal nail clipping results in high prevalence of contamination. This can be overcome by proper cleaning of the nail plate with alcohol before sample taking. In our study, majority of onychomycosis grown NDMs consisting of *Aspergillus* (13/26%) species and *Fusarium* (10/20%). Therefore, repeated nail samplings are deemed needed in order to detect the true pathogenic agents.

In this study, nearly half of the fungal culture positive samples were negative in PCR test. Besides, some fungal culture positive and PCR positive samples yielded discordant fungal species. The inconsistencies may be attributed by insufficient fungal cells in the PCR sample, improper storage of the specimen or late arrival of sample to the lab. Sample processing for fungal cultures is ideally within 2 hours following sample collection.[33] Incorrect technique of sample collection may also affect the culture results significantly. Lastly, improper techniques of PCR by lab assistant also contribute to negative PCR results. According to studies done by in Sweden[34] and India[35], the detection rate of dermatophytes for the fungal PCR in nail specimens with suspected dermatophytosis was 44% and 48%, respectively. This was consistent with our detection rate of around 50%. The low detection rate in these studies was attributed to the mutations in the fungal strains recognised by the PCR hybridising[38] and inhomogeneous distribution of fungal DNA in the sample collected.[35] Other possibility included the use of suboptimal methods for DNA extraction.[36] The method of DNA extraction should selectively accumulate the fungal DNA and at the same time reduce human DNA. The larger fungal DNA volume, the more for amplification and hence the more sensitive. On the other hand, the more human DNA in clinical sample used for amplification will resulting in cross-hybridisation and inhibition of the PCR.[36]

Fungal culture remains the gold standard for the microbiological diagnosis of fungal infections and the price to perform a fungal culture is much cheaper compared to PCR test. Nevertheless, the turn-around-time to perform fungal PCR test was shorter (within days) compared to fungal culture (within weeks). Currently, fungal PCR is not widely available for commercial use.

Among the local Melaka population, most patients with dermatomycoses will initially visit general practitioners. Hence, the diagnosis is often clinically based. Laboratory investigations such as fungal culture are rarely performed at primary health care clinics. The turn-around-time (TOT) for fungal cultures is 7 to 21 days. On the other hand, PCR test may be able to detect the superficial fungal infection at a shorter TOT with presumed a more accurate result. However, this test is very costly and technically highly demanding. Our study on the other hand showed that the detection rate of PCR was nearly 50% lower than the gold standard test culture. Hence, the routine use of PCR in the management of superficial fungal infection may not be cost effective at present. Our study nevertheless helped us to monitor the pathogenic fungus encountered locally in superficial fungal infection. This is especially important for onychomycosis where NDM were the most common aetiology observed. The treatment regime for NDM onychomycosis should be extended and prolonged.[37] Accurate diagnosis is important and essential to ensure the treatment is targeted.

The limitations of this study include small in sample size and short study duration. Our current study only involved patients visited to Hospital Melaka. A larger study population with a longer study duration together with involvement of primary healthcare clinics is needed to ensure the study results are more representative of the whole Malaysian population. In addition, due to the budget limitation, we could not perform PCR tests for culture negative sample. Hence the sensitivity, specificity, positive and negative predictive values could not be determined. A study done in Italy has shown a high positive predictive value of 100% and a negative predictive value of 75.9% for the diagnosis of onychomycosis.[38] Therefore, fungal PCR was useful as a confirmation step and for urgent case in diagnosis of onychomycosis.[38] Ndiaye et al in another study reported that

multiplex real-time PCR assay had a 73.3% positive predictive value and a 90.2% negative predictive value in detecting dermatophytes in human hair samples.[39]

CONCLUSION

Trichophyton rubrum was the main causative fungus of tinea corporis/cruris/pedis while tinea capitis was mainly caused by *Microsporum canis* in Hospital Melaka. Non dermatophyte moulds were mainly isolated in onychomycosis in our study.

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ORIGINAL ARTICLE

Association of dengue serotypes and its complications: a retrospective cohort study

Lau Qinglin, MRCP[1], Lee Zhao Ming, MRCP[3], Tan Chen Yong, MRCP[1], Anusha AP Shunmugarajoo, Mmed[2], Azureen Bt Azmel, Mmed[2], Yap Soong Yiing, MPH[4]

[1]Internal Medicine Department, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [2]Infectious Disease Unit, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [3]Internal Medicine, Hospital Duchness of Kent, Ministry of Health, Sabah, Malaysia , [4]Clinical Research Center (CRC), Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia

ABSTRACT

Introduction: Dengue fever is an arthropod-borne disease and has a wide clinical spectrum. It is hypothesised that dengue serotypes could be a possible factor for such phenomena and therefore be a possible predictor for the development of severe dengue.

Method: A retrospective cohort study was done to explore the association between dengue serotypes and the various complications. All patients who underwent dengue serotyping from 1st January to 31st December 2018 in Tengku Ampuan Rahimah Hospital were selected. Serotypes were randomly done for admitted dengue patients. Notes were then retrieved for data collection. Secondary outcomes like length of stay and highest lactate level were also studied. Data analysis was done using SPSS version 20.

Result: A total of 193 patient records were included in the analysis. Chi-square test for independence indicated that the proportion of dengue complications between male and female were significantly different ($\chi^2(1) = 11.37$, $p = 0.001$). Dengue serotype was not associated with the development of dengue complications, total number of dengue complications, length of admission, lactate level and survival among the serotypes. Results of the binary logistic regression showed that men have thrice the odds (AOR = 3.3, 95% CI: 1.6 6.7) for developing dengue complications. One patient was found to be co-infected with serotype 2 and 3.

Conclusion: Our study did not reveal any association between the different dengue virus serotypes and its complications. Therefore, all dengue infection should be approached with equal meticulousness. There are possibilities that apart from serotype, dengue genotype and lineage would determine clinical outcome. However, more studies are required to study such associations.

KEYWORDS:
Dengue, dengue complications, serotypes

INTRODUCTION

Dengue is an arthropod-borne infectious disease caused by the dengue virus. The virus consists of four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) and is transmitted through bites of infected Aedes mosquitoes.

Being endemic in tropical and sub-tropical countries, dengue is a major public health issue in Malaysia with an incidence 245 per 1000 population in the 2018.[1] The incidence of dengue has alarmingly risen seven-fold from the year 2000 to 2010 and peaked in 2019 with an incidence of 399 cases per 10,000 population.[1,2] It was estimated that Malaysia spent around USD175.7 million annually on the treatment and prevention measures of dengue.[3]

The dengue virus is from the genus *Flavivirus* which falls under the family of *Flaviviridae*. Dengue virus was first identified and isolated in 1943 in Japan. That specific isolated virus is now referred to as the dengue virus 1 or DEN 1. Since then, dengue virus has been divided into four serotypes based on the interaction with the antibodies in the human blood serum.[4] Such discovery is followed by the question of clinical outcomes among patients who are infected with different serotypes. Different dengue serotypes had been observed to be associated with different complications as reported by Vincente CR et al.[5] It is noteworthy that patients with DENV-2 appeared to have a higher tendency of progression to severe dengue than among those of DENV-1 and DENV-4.[5] A retrospective study conducted in Thailand also revealed that DENV2 was the most frequent serotype isolated from patients suffering from haemorrhagic fever and dengue shock syndrome.[6]

Hospital Tengku Ampuan Rahimah (HTAR) is considered to be one of the busiest tertiary hospitals in the country and has a high number of dengue fever admissions. In this retrospective cohort study, we explore the association between different dengue serotypes and dengue complications. In addition, we examined the type complications encountered and length of hospital stay among patients of different dengue serotypes in HTAR.

MATERIALS AND METHODS

Study Design and Population

In HTAR, Real-Time Quantitative Reverse Transcriptase Polymerase Chain Reaction (RT-qPCR) serotype identifications were done for dengue patients who were admitted to the intensive care unit (ICU) and randomly selected dengue patients from the dengue wards. In this retrospective cohort study, we compiled a list of all 230 patients with dengue serotypes record from microbiology laboratory spanning from 1 January 2018 till 31 December

This article was accepted: 21 May 2023
Corresponding Author: Qinglin Lau
Email: qinglinlau@gmail.com

2018. Patients under the age of 18 years with missing case notes were excluded from the study. From this list of 193 patients, we retrieved patients' case notes and retrospectively analysed the associated dengue complications, highest lactate level, length of stay (LOS) in hospital and outcome (alive/dead).

Outcome Measures

Our primary goal is to determine any correlation between serotypes and each dengue complication. In addition, we also investigated for possible linkage between average number of complications for each serotype, the highest lactate levels, average LOS and the number of mortalities according to serotype. Patients' clinical classification and complications were clinically diagnosed by the physicians according to the 2012 World Health Organisation (WHO) guideline for dengue. Based on WHO and local guidelines, multiple complications are decided as the study outcome. For haemophagocytic lymphohistiocytosis (HLH), patients with serum ferritin ≥ 20,000 µg/L or ≥ 10,000 µg/L plus organ impairment were included. For carditis, patients with CK ≥ 1000U/L, raised troponin or evidence of carditis via echocardiographic imaging were included. To fulfil the complication of hepatitis, patients will have ALT or AST ≥ 1000U/L. In the case for polyuria, patients with urine output of more than 3 L/day were included. Lastly, for complications such as encephalitis, acute kidney injury (AKI), bleeding (occult/overt) or plasma leakage (ascites/pleural effusion), we included patients who were clinically diagnosed as such by attending clinicians.

Statistical Analysis

Statistical analysis was performed using the Statistical Analysis Software Version 20 (SPSS 20).

RESULTS AND ANALYSIS

A total of 193 patient records were included in the analysis, one dengue patient was found to be co-infected with serotype 2 and 3. The age of the subjects varied from 18 to 85 years, with an average age of 39.5 years (SD 16.0). Majority of the subjects were female (55.4%), native (51.8%), were infected with dengue serotype 3 (40.4%) and developed dengue related complications (71.5%).

Among the complications studied, it was found that a third of subjects developed plasma leakage (34.2%). The second most common complication encountered was bleeding (24.9%), followed closely by carditis (21.2%), HLH (16.1%), AKI (14%), polyuria (10.9%), hepatitis (9.8%) and encephalitis (9.3%). Complications developed were not mutually exclusive as many subjects developed more than one complication during their hospitalisation. Figure 1 shows the number of complications developed by subjects in this study. The sociodemographic details of the study population and complications are presented in Table 1.

Chi-square test for independence indicated that the proportion of dengue complications between male and female were significantly different ($\chi2(1) = 11.37$, $p = 0.001$). Lactate levels were significantly associated with dengue complication. The length of stay was also prolonged when dengue complication occurs. Age, ethnicity and dengue serotype did not influence this outcome.

Age, ethnicity and dengue serotype did not affect the development of complications for both univariable and multivariable analysis. Interaction between lactate levels and length of stay was noted, thus length of stay was not included in the multiple logistic regression analysis. Male gender and higher lactate levels were found to be significant predictors for dengue related complications after adjusting for age, ethnicity and dengue serotype.

(Male adjusted odds ratio [AOR]: 3.07 [1.43, 6.56] when compared to female; lactate levels 2.1-3.0 AOR: 4.15 [1.86, 9.24]; lactate levels >3.0 AOR: 11.25 [4.17, 30.36] when compared to lactate levels of 2.0 and below)

Further analysis showed that men had 2.65 times risk of bleeding (95% CI: 1.35, 5.19), 3.51 times risk of acute kidney injury (95% CI: 1.45, 8.48) and 4.68 times risk of developing carditis (95% CI: 2.18, 10.05) when compared to women in this study. Other complications studied which were plasma leakage, HLH, polyuria, encephalitis and hepatitis were found to be not significantly affected by gender.

Dengue serotype was not associated with neither development of AKI, carditis, HLH, bleeding, encephalitis, hepatitis, nor plasma leakage using Pearson Chi-square test (Figure 2).

Chi-square test for independence indicated that there were no significant associations between dengue serotype with lactate levels and number of dengue complications, whereas Fischer exact test analysis found that this variable was not associated with the overall survival of dengue patients. As the distribution of length of stay among the serotypes was skewed, Kruskal-Wallis test was used to show no significant difference for duration of hospitalisation between the different serotypes ($\chi^2(2) = 1.45$, $p = 0.483$).

DISCUSSION

In Malaysia, although all four serotypes can be isolated from the community acquired infection, DENV1 and DENV2 are the predominant serotypes seen. The number of patients with DENV3 and DENV4 infection has reduced since 2013. Notably, the number of DENV4 serotypes infection was not captured from 1996 to 2000.[7] The absence of DENV4 infection is consistent in our study also. However, our cohort showed that DENV3 was the most prevalent serotype to infect our cohort.

The current study focuses on the isolated serotypes and its complications. Based on our analysis of these 193 dengue patients in HTAR from the year 2018, there had been no or negligible association between the serotypes and types of complications encountered. In terms of disease severity, there seemed to be no marked difference in the highest lactate levels recorded between each serotype.

There are myriad of studies studying DENV serotypes and dengue severity but their discoveries were not consistent. A

Table I: Sociodemographic characteristics of dengue patients and dengue related complications

Variable	Complications		*p* value
	No	Yes	
No. of persons	55 (28.5%)	138 (71.5%)	
Age (years)			0.236[a]
median (IQR)	34.0 (27.0)	38.0 (25.0)	
Gender			0.001[b]
Male	14 (25.5%)	72 (52.2%)	
Female	41 (74.5%)	66 (47.8%)	
Ethnicity			0.936[b]
Native	30 (54.5%)	70 (50.7%)	
Chinese	6 (10.9%)	14 (10.1%)	
Indian	14 (25.5%)	38 (27.5%)	
Others	5 (9.1%)	16 (11.6%)	
Dengue serotype			0.488[b]
1	16 (29.1%)	34 (24.6%)	
2	15 (27.3%)	50 (36.2%)	
3	24 (43.6%)	54 (39.1%)	
Lactate levels (mmol/L)			<0.001[b]
2.0 and below	30 (54.5%)	22 (15.9%)	
2.1-3.0	18 (32.7%)	56 (40.6%)	
3.1-4.0	4 (7.3%)	48 (34.8%)	
4.1 and higher	3 (5.5%)	12 (8.7%)	
Outcome			0.559[c]
Survived	55 (100.0%)	135 (97.8%)	
Died	0 (0.0%)	3 (2.2%)	
Length of Stay (days)			0.007[a]
median (IQR)	4.0 (2.0)	5.0 (3.0)	

IQR: interquartile range
[a]: Mann-Whitney U test
[b]: Pearson chi-square test
[c]: Fischer exact test

Table II: Results of univariable and multivariable analysis of study variables with complications

Variable	Crude OR (95% CI)	*p* value
Age (years)	1.01 (0.99, 1.03)	0.354
Gender		0.001
Female	1.00 (Ref.)	
Male	3.20 (1.60, 6.39)	
Ethnicity		0.936
Malay	1.00 (Ref.)	
Chinese	1.00 (0.35, 2.85)	1.000
Indian	1.16 (0.55, 2.46)	0.692
Others	1.37 (0.46, 4.09)	0.571
Dengue serotype		0.490
3	1.00 (Ref.)	
1	0.94 (0.44, 0.23)	0.883
2	1.48 (0.70, 3.14)	0.305
Lactate levels (m mol/L)		<0.001
2.0 and below	1.00 (Ref.)	
2.1 to 3.0	4.24 (1.98, 9.11)	<0.001
3.1 and higher	11.69 (4.49, 30.43)	<0.001
LOS (days)	1.17 (1.01, 1.37)	0.043

cross-sectional study by Vincente CR et al. in Brazil of 485 dengue cases revealed that patients with Serotype 2 had a higher proportion of severe dengue as compared to those of Serotype 1 and 4.[5] This result was corroborated by other previous studies.[8-13]

However, there were also studies with conflicting results. In 2011, a study done on hospitalised cases in Vietnam revealed that Serotype 1 and 2 had similar chances of progressing to dengue haemorrhagic fever.[14] Fox et al suggest that patients with DENV 1 had a higher probability of developing dengue haemorrhagic fever as compared to those with Serotype 2.[15] Suppiah, et al showed that patients infected with DENV2 would developed severe dengue more frequently but also discussed about the role of genotypes affecting clinical manifestations of dengue infection.[16] Yung et al. discussed about the possibility that the same serotype may have different genotype which results in a different clinical outcome.[17] E-envelope sequencing were done to identify genotypes of specific serotypes. The author showed that the DENV 2 serotype of a cosmopolitan genotype circulating in Singapore and Malaysia was different from the

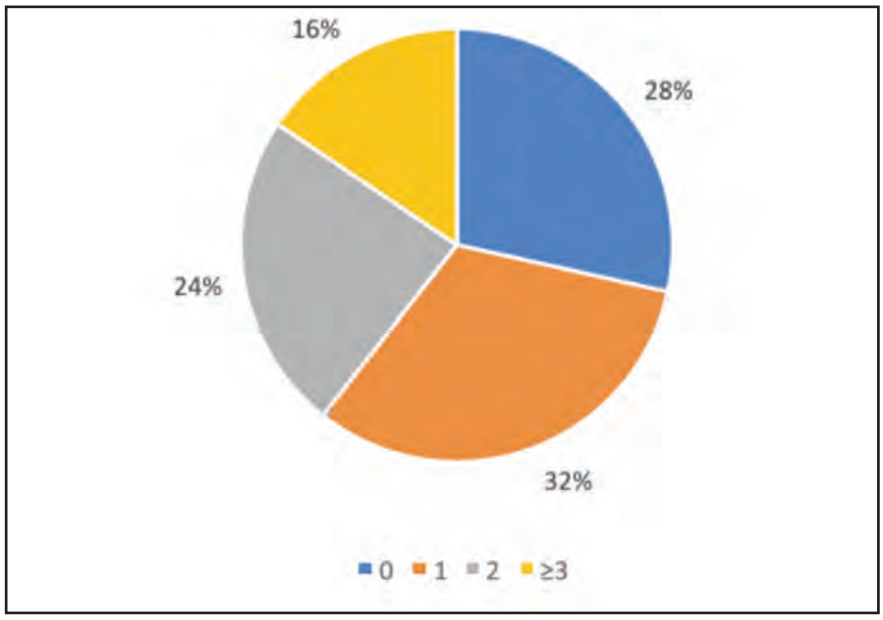

Fig. 1: Number of dengue related complications by subjects

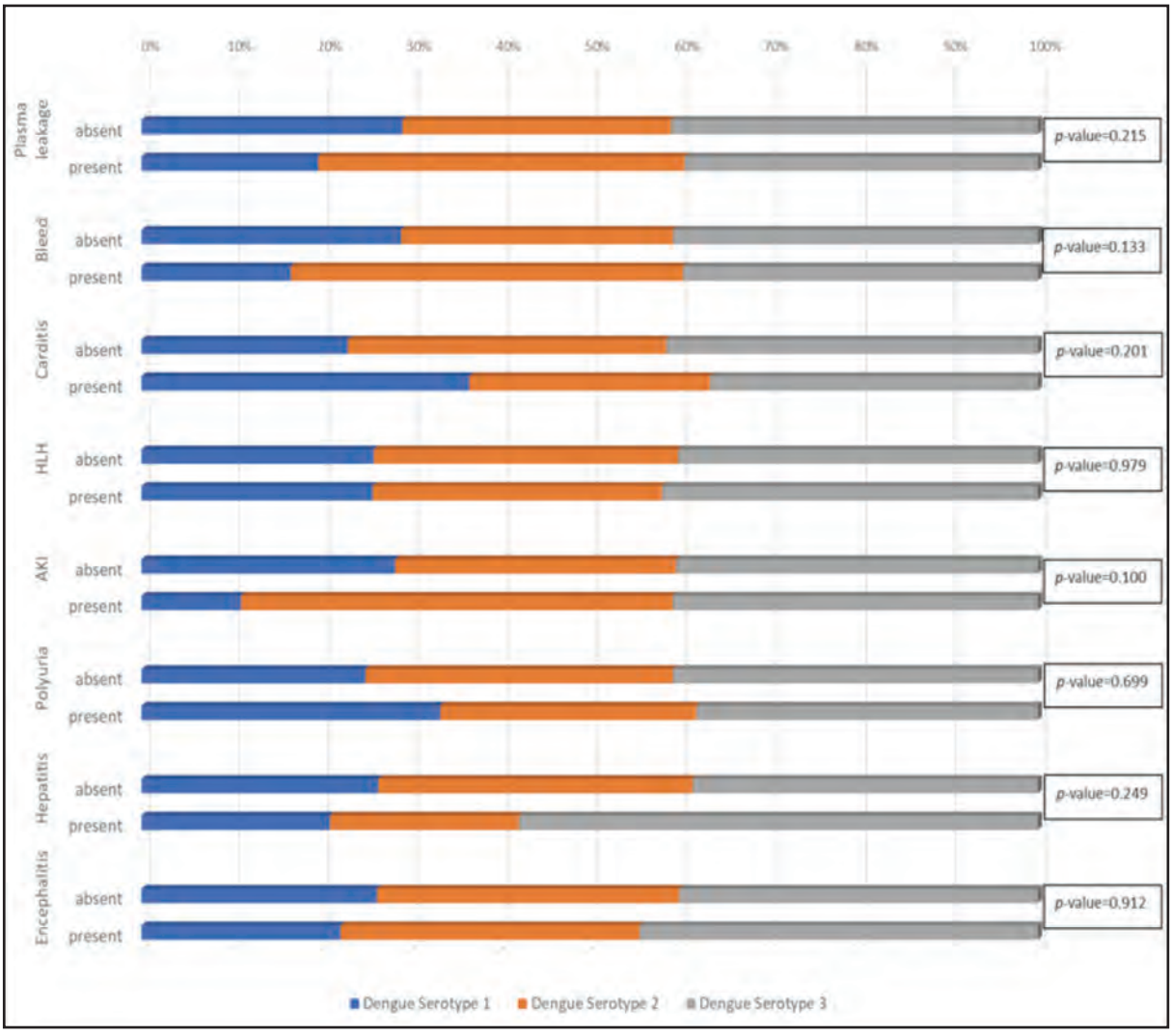

Fig. 2: Association of dengue complications with dengue serotype

American/Asian genotype in Brazil and can be the reason for the reduced severity observed.[17] Jiang et al further studies the lineage of DENV2 genotype and the risk of developing haemorrhage and shock. They concluded that Malaysia/Indian subcontinent genotype for DENV2 may be less virulent.[18] It is possible that due to the genotypic variability of the DENV in our population, the association of DENV serotype and severity or complication is less straightforward.[16] More studies need to be done to identify DENV serotypes, genotypes and lineage in our population.

Our study showed that there is a higher proportion of female who has been admitted for dengue infection. This could be due difference in health care-seeking behaviour. Female have been reported to visit healthcare provider more and would translate to a higher pick-up rate.[19-21] The increased dengue cases for female is reflected by a studies in Puerto Rico and Mexico which showed that female made up a slight majority of adult dengue cases.[22,23] However, this is in contrast with Singapore, which had a larger proportion of men among those who had dengue infection reported from year 2000 to 2005.[24] A local study by Shekhar et al also observed a higher dengue infection rate in males.[24] It is important to note that the studies above are epidemiological studies and therefore may reflect differently from our study which is hospital based. Despite the increase in female cases, our study revealed that men are at higher risk of having dengue complication regardless of serotypes. Higher incidence of dengue haemorrhagic fever and mortality among males has been reported by Shekhar et al.[24] Md-Sani et al studied 199 patients with severe dengue patients and found that two-third of his cohort was noted to be male.[25] Fatal dengue cases were also observed more frequently in male as noted by Dakeek et al in Yemen.[26] It is likely that such findings may be due to the fact that men are likely to "underreact" to illness leading to late diagnosis and a more severe presentation.[27]

One patient in our study had coinfection with Serotype 2 and 3. She was a 17-year-old female who suffered from plasma leakage as a result of a complication from dengue. However, her highest lactate level was 1.5 mmol/L and she was discharged well after spending 4 days in the hospital.

DENV coinfection is an interesting phenomenon. The very first reported case of coinfection with different dengue serotypes was in Puerto Rico in the year 1982.[28] Although there had been reports from other countries, at the time of this writing, this is the only the second known published report of concurrent infections in Malaysia. Suppiah et al described one case of DENV1 and DENV2 coinfection in 2015. The study however did not describe any association between such occurrence and dengue complications.[16] An analysis of the different dengue serotypes coinfection during an outbreak in India identified nine patients with DENV co-infection. It showed that six out of the nine subjects had dengue haemorrhagic fever but did not conclude any statistical significance.[29] In contrast, a study in 2011 by Martin et al involving an outbreak in in Brazil revealed that patients with co-infection tend to develop severe dengue or minor haemorrhagic phenomena. The report also concluded that there is an increase of alarm sign in those with two serotype co-infections.[30]

We postulate that the patients with DENV co-infection may have been exposed to a single mosquito which was heteroserotypic. A study in Southern Thailand which involved the capture of Aedes sp. mosquito in the fields was done in 2005. Viral RNA was extracted from all the captured mosquitoes. The researchers revealed three mosquitoes which were infected with two different serotypes. It is postulated that such phenomena could have occurred when the vector feed on dengue patients, each with different serotype thus exposing it to different serotypes or vector feeding on patients with existing heteroserotypic infection.[31] Nevertheless, we believe such occurrence would only be likely in a community deemed to be hyperendemic with dengue virus as in our population.[32]

In our study, patients with different serotypes appeared to have similar average length of stay LOS. A longer LOS result in higher healthcare cost incurred for food, bed occupancy and treatment. This corresponds to our finding of a similar degree of severities across all serotypes. A multivariate analysis by Mallhi et al. of dengue patients attending tertiary care centres revealed that dengue haemorrhagic fever, coagulopathy and multiple organ dysfunctions were independently associated with prolonged hospitalisation.[33] Such finding is consistent with our study.

Serum lactate has long been used to be a marker of end-organ hypoperfusion or shock. Due to the fact that dengue shock syndrome is a well-known complication of severe dengue, lactate can be a good predictor to indicate severity.[34] M Gupta et al while studying a few prognostic markers went as far as to report that lactate was found to be the best prognostic marker for mortality for severe dengue.[36] Our study reaffirms this notion by revealing the association between high lactate level and dengue complications.[35-37]

CONCLUSION

Dengue virus infection, regardless of the serotypes, should be approached identically and treated with an equal level of meticulousness as all of them appeared to have similar severity. More studies can be done to explore the inherent pathologic nature of the dengue serotype, such as dengue genotypes and lineage. Further studies in regard to dengue serotype co-infection and complications should be pursued due to our hyperendemic circumstances.

STUDY LIMITATION

This was a retrospective cohort study of dengue patients in HTAR in the year 2018 and the authors are aware of the inherent limitation of a small sample size and low mortality rate to draw any consequential conclusion from this study. Not all dengue patients who were admitted in 2018 were included in this study as PCR serotypes identification was done only for dengue patients who were admitted to the intensive care unit (ICU) and randomly selected dengue patients from the dengue wards.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We are also grateful to Dr Eashwary Mageswaren, head of medical department, Hospital Tengku Ampuan Rahimah, Dr Katrina Lau Kieng Huong, Consultant General Physician in Hospital Tengku Ampuan Rahimah and Dr Tan Thai Lun, General Physician in Hospital Tengku Ampuan Rahimah for their advance review and feedback of this article.

DECLARATION

This study has no conflict of interest and is not funded by any organisation.

ETHICAL APPROVAL

This study was registered with National Medical Research Register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) and the Ministry of Health (MOH). MREC Approval Letter 22-01488-KLB (1) dated 26 September 2022. NMRR ID 22-01488-KLB

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Pulmonary thromboembolic disease associated with COVID-19 infection: a comparison between geriatric and non-geriatric populations

Thai Lun Tan, MRCP[1], Noor Emillia Binti Illa, DrRad[2], Siew Ying Ting, MD[3], Niny Hwong Perng Ling, MMed[1], Nor Hakima Binti Makhtar, MMeD[4], Xavier Sim Yoon Han, MRCP[5], Nor Asiah Binti Muhamad, MComm[6], Shoen Chuen Chiew, BPharm[3]

[1]Internal Medicine Department, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [2]Radiology Department, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [3]Clinical Research Centre, Hospital Seri Manjung, Ministry of Health, Perak, Malaysia, [4]Geriatric Unit, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [5]Haematology Unit, Hospital Tengku Ampuan Rahimah, Ministry of Health, Selangor, Malaysia, [6]Evidence-Based in Healthcare, National Institutes of Health, Ministry of Health, Selangor, Malaysia

ABSTRACT

Introduction: The magnitude of Coronavirus Disease 2019 (COVID-19) infection among the elderly population is expected to rise. Our study compares the clinical and computed tomographical (CT) features of pulmonary thromboembolic (PTE) disease associated with COVID-19 infection in geriatric and non-geriatric cases, and explores the 60-day mortality rate in these two groups.

Materials and Methods: We conducted this retrospective cross-sectional study in Hospital Tengku Ampuan Rahimah, Selangor, Malaysia. Patients admitted in April 2021 and May 2021 with concomitant COVID-19 infection and PTE disease were included. Demographic, clinical and laboratory data were retrieved, whilst CTPA images were analysed by a senior radiologist.

Results: A total of 150 patients were recruited, comprising 45 geriatric patients and 105 non-geriatric patients. The prevalence rate of hypertension, diabetes mellitus and dyslipidaemia were higher among the geriatric cohort. Evidently, the percentage of patients with fever and diarrhoea were significantly higher among the non-geriatric cohort. The geriatric cohort also recorded a significantly lower absolute lymphocyte count at presentation and albumin level during admission. Despite earlier presentation, the geriatric cohort suffered from more severe diseases. Analysis of the CT features demonstrated that the most proximal pulmonary thrombosis specifically limited to the segmental and subsegmental pulmonary arteries in both cohorts. The elderly suffered from a significantly higher in-hospital mortality rate and their cumulative probability of survival was significantly lower.

Conclusion: Typical COVID-19 symptoms may be absent among the elderly, prompting a lower threshold of suspicion during the COVID-19 pandemic. Additionally, the elderly demonstrated a higher probability of adverse outcomes despite earlier presentation and treatment.

KEYWORDS:
COVID-19, geriatric vs. non-geriatric populations, pulmonary thromboembolic disease

INTRODUCTION

Coronavirus disease 2019 (COVID-19) virus which is caused by the novel SARS-CoV-2 was first reported in Wuhan, Hubei Province in December 2019, has evolved to become a pandemic of global scale.[1,2] SARS-CoV-2 is a single-stranded RNA virus which binds the angiotensin-converting enzyme-2 receptors on the endothelial cells, especially within the kidneys, heart, lungs and liver.[3] The damage to the endothelial cells can lead to widespread thrombosis that cause numerous thrombotic complications such as deep vein thrombosis, pulmonary thromboembolic (PTE) disease, myocardial infarction, stroke and disseminated intravascular coagulation.[4,5] In severe case, it can lead to acute respiratory distress syndrome or multiorgan failure.[6] Demographics and comorbidities that are associated with COVID-19 infection include older age, male sex, ethnicity, diabetes mellitus, systemic hypertension and chronic cardiorespiratory disease.[7]

There were 601,189,435 confirmed COVID-19 cases and total deaths related to COVID-19 has amassed to 6,475,346 worldwide by September 2022.[8] The elderly populations are at the forefront on this onslaught and studies have consistently proven that they are at the risk of adverse outcomes and fatal disease.[7,9] In recent years, studies on PTE disease have gained renewed interest since the emergence of COVID-19 infection. In the seminal papers by Khismatullin et al and Loo et al, it was postulated that PTE disease associated with COVID-19 is driven by in-situ thrombosis caused by immune system hyperactivation that is distinctly different from the conventional PTE disease.[10,11]

It is well established that the occurrence of PTE disease during COVID-19 infection portends a negative survivor outcome, especially among the geriatric populations.[12] Moreover, the later would continue to bear the brunt of this ongoing

This article was accepted: 17 May 2023
Corresponding Author: Dr Tan Thai Lun
Email: tanthailun@gmail.com

COVID-19 pandemic which is unlikely to disappear from the community in the foreseeable future.[13] The aim of this study is thus to compare the clinical and computed tomographical (CT) features of PTE disease associated with COVID-19 infection between geriatric and non-geriatric cases as well as to explore the 60-day mortality rate between these two groups.

MATERIALS AND METHODS

Study Setting

Hospital Tengku Ampuan Rahimah (HTAR) is a tertiary hospital located in the royal Klang district, Selangor, Malaysia. HTAR had been providing integrated care to both non-Covid and Covid infected cases since 13th January 2021. During the study period, Klang Valley was one of the worst affected regions in Malaysia with thousands of new COVID-19 cases reported daily and the number of hospitalized cases treated in HTAR was ranked the third highest in Klang Valley, after Hospital Sungai Buloh and Hospital Kuala Lumpur.

Study Design and Data Collection

This was a retrospective cross-sectional study conducted among adult COVID-19 patients with CTPA confirmed PTE who were admitted in HTAR between 1st April 2021 and 31st May 2021. We had screened a total of 197 patients, which involved all the hospitalised adult COVID-19 patients who had CTPA done for suspected acute PTE disease within the study period. Patients aged ≥ 18-year-old diagnosed with COVID-19 either through real time Reverse Transcriptase-Polymerase Chain Reaction (rRT-PCR), GeneXpert test or rapid antigen test from nasopharyngeal swab or lower respiratory tract sample with CTPA confirmed PTE were included in this study. In total, 47 subjects were excluded due to the following reasons: without CTPA evidenced PTE (34 cases), at own risk discharge (3 cases), severe CTPA image artefacts (1 case), onset of COVID-19 infection more than 30 days at presentation (2 cases), hospital acquired COVID-19 infection (2 cases) and incomplete or missing clinical notes (5 cases). Therefore, a total of 150 patients were included in the analysis.

Clinical and Laboratory Data

Clinical data and laboratory data were extracted from the clinical case notes and electronic medical systems. We defined "elderly" as whom chronological age is ≥ 65 years (completed age upon admission) and they were categorised as geriatric cohort. Conversely, anyone aged below 65 years was grouped as non-geriatric cohort. For each COVID-19 patient, the clinical and laboratory data were retrieved retrospectively from the case notes as well as the online laboratory systems by two physicians (Tan TL and Niny H).

COVID-19 day of illness was calculated from the onset of clinical symptoms compatible with COVID-19 infections. However, if the clinical history was unclear or the patient was asymptomatic, then the first day of illness would be calculated from the date when the COVID-19 confirmatory test first became positive. The definitions of COVID-19 clinical stages were as follow: category 1-asymptomatic; category 2-symptomatic but no pneumonia; category 3-symptomatic with pneumonia; category 4-symptomatic with pneumonia and requiring supplement oxygen; category 5a-requiring non-invasive ventilation including high flow nasal cannula and category 5b-requiring mechanical ventilation with or without other organ failures.[14]

With reference to our institutional protocols, we developed the following anticoagulation regimen definitions. Prophylactic anticoagulation regimen was defined as follows: (a) subcutaneous enoxaparin 40 to 60 mg daily (if eGFR ≥30 ml/min/1.73 m^2) (b) subcutaneous enoxaparin 20 to 30 mg OD (if eGFR < 30 ml/min/1.73 m^2) and (c) subcutaneous unfractionated heparin 5000 units q12 hourly or q8 hourly. Therapeutic anticoagulation regimen was defined as follow: (a) subcutaneous enoxaparin 1 mg/kg/BD or 40 to 60 mg BD (if eGFR ≥ 30 ml/min/1.73 m^2); (b) subcutaneous enoxaparin 1 mg/kg/OD or 40 to 60 mg OD (if eGFR < 30 ml/min/1.73 m^2); (c) warfarin with INR ranged 2 to 3 and (d) direct oral anticoagulation therapy as per drug insert recommendation. Any dose in between prophylactic and therapeutic range were considered as intermediate anticoagulation. In the circumstances where the body weight was unavailable, the physician would exert his discretion to determine the anticoagulation regimen given.

In addition, we examined the bleeding complications related to anticoagulant therapy. We regarded the following events as major bleeding: (i) fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or (ii) intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells. If patient fulfilled criteria (ii) in the absence of an apparent bleeding cause, the physician would exert his discretion to decide whether the cause of severe anaemia was attributed to major occult bleeding. Additionally, bleeding events that preceded the initiation of anticoagulant therapy were excluded. Any bleeding event that did not fulfil the-before-mentioned criteria was regarded as minor bleeding complication (adapted from International Society on Thrombosis and Haemostasis criteria).[15]

Acute transaminitis was defined as a two-fold increase in serum aspartate transaminase (AST) or serum alanine transaminase (ALT) level from baseline whilst acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥ 26.5 µmol/L within 48 hours or increase in serum creatinine by 1.5 times baseline.[16]

The primary outcome measure was 60-day mortality after the onset of COVID-19 infection. Due to the retrospective nature of the study, we did not attempt to determine whether 60-day mortality was attributable to the COVID-19 infection. Out of hospital death was confirmed with National Death Registry.

Radiological Data

(a) CT image acquisition and analysis

The CTPA examination was performed on 64 slice multi-detector CT scanners (Toshiba Aquillion CX). The whole chest was craniocaudally scanned from lung apices to the lowest hemidiaphragm for each patient in the supine position in

single breath hold if possible. The scan parameters were as follow: tube voltage of 120 kV, tube current of 100 to 300 mAs, collimation of 0.6 to 0.625 mm, table speed of 39.37 mm/s, and gantry rotation time of 0.5 s. A weight adjusted non-ionic iodinated contrast medium (Ultravist 370) was given with a 40 ml saline flush via a mechanical dual power injector. To optimise the intraluminal contrast enhancement, automatic bolus-tracking technique was used and targeted at the level of the main pulmonary artery with a trigger threshold of 120 HU. Image was reconstructed with a thickness of 1 mm and an increment of 1 mm or 1.25 mm.

(b) Image interpretation

All CTPA images were reviewed by a senior radiologist (Dr Emilia, principal COVID CT thorax analyst with 6 years' experience). Under the mediastinal window setting (width, 250 HU; level, 50 HU), the CTPA images would be analysed. Lung window with a width of 1500 HU and level of 500 HU was set. The anatomical sites of the acute pulmonary thromboembolism were reported based on the most proximal anatomic location. For each PE location, the degrees of lung involvement were reported as multi-lobar (unilateral), multi-lobar (bilateral) or single lobar (unilateral). Lastly, the severity of COVID-19 pneumonia and organising pneumonia changes was reported based on the total areas of lung parenchyma involvement. We separated the aforementioned severity into four categories based on the extent of pneumonia changes detected on CT images in the lung window: (1) minimal (< 25%), (2) mild (25-50%), (3) moderate (51-75%) and (4) severe (>75%).[17]

Statistical Analysis

We performed data analysis using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp.). Geriatric and non-geriatric cohorts were compared using Pearson Chi-square, Fisher's exact test, Student t test and Mann-Whitney U test. Kaplan-Meier curve was used to estimate the probability of survival at 60 days for both geriatric and non-geriatric cohorts. Log-rank test was used to compare if there was any difference between both cohorts in the probability of 60-day mortality. The event of interest was death cases that occurred within 60 days after the onset of COVID-19 infection. For all statistical comparisons, a p value < 0.05 was considered statistically significant.

RESULTS

Comparison of Socio-demographic and Clinical Characteristics Between the Geriatric and Non-geriatric Cohorts

As illustrated in Table I, a total of 150 patients with CT confirmed pulmonary thromboembolic disease were recruited during the study period, which was represented by 45 (30.0%) geriatric patients and 105 (70.0%) non-geriatric patients. The median age of the geriatric cohort was 69 years (IQR 67.0-73.0), while the median age of the non-geriatric cohort was 54 years (IQR 44.5-60.0). Evaluation of gender distribution showed that majority of the study populations were male in both geriatric and non-geriatric cohorts (57.8% vs. 61.9%; p=0.635).

A review of the prevalence of comorbidities demonstrated that 73.3% (n=110) of patients had at least one comorbidity. The prevalence rate of hypertension (62.2% vs. 47.6%) diabetes mellitus (55.6% vs. 39.0%) and dyslipidaemia (24.4% vs. 13.3%) in geriatric cohort were higher compared to non-geriatric group. In contrast, subjects with underlying end stage renal disease (n=4, 3.8%) and malignancy (n=1, 1.0%) only occurred among the latter group. Overall, the differences observed were not statistically significant.

Almost all patients were symptomatic at presentation (n=149, 99.3%) and the commonest symptoms were cough (n=115; 76.7%), fever (n=106; 70.7%) and shortness of breath (n=100; 66.7%). Evidently, the percentage of patients with fever (53.3% vs. 78.1%; p=0.002), diarrhoea (17.8% vs. 39.0%; p=0.011) and fatigue (35.5% vs. 14.3%; p=0.003) were significantly different between the geriatric and non-geriatric cohorts. The median temperature at presentation was generally lower among the geriatric cohort in comparison to non-geriatric cohort (median 37.5, IQR 36.7-38.6 vs. median 38.1, IQR 37.1-38.8; p=0.054). Also, none of patients had clinical deep vein thrombosis.

In another note, both day of illness at presentation (median 4, IQR 2.0-6.0 vs. median 6, IQR 4.0-8.0; p=0.001) and day of illness during CTPA (median 9, IQR 6.0-12.0 vs. median 10, IQR 8.0-14.0; p=0.005) among geriatric cohort was significantly earlier as compared to non-geriatric cohort. Though the geriatric cohort presented earlier to the hospital, their categories of illness at presentation were more severe as indicated by higher percentage in category 4b to 5b (42.2% vs. 29.6%). Geriatric cohort had higher percentage of category 5b during CTPA examination as well (26.7% vs. 14.3%). Despite of this, the difference in the category of illness at presentation and during CTPA were not statistically significant between the two cohorts.

Comparison of treatment received during or prior to CTPA examination showed that the proportion of patients on inotropic support was significantly higher among the geriatric cohort (24.4% vs. 11.4%; p=0.043). Other treatments received which included immunomodulators and favipiravir treatment were comparably similar between the two groups. It is noteworthy that almost all patients received systemic steroidal treatment (n=148, 98.7%), as well as prophylactic, therapeutic or intermediate anticoagulation therapy (n=144; 96.0%) prior CTPA examination.

Comparison of Clinical and Survival Outcomes Between the Geriatric and Non-Geriatric Cohorts

As shown in Table I, treatment received throughout admission suggested that the geriatric cohort was generally more ill as the percentage of inotropic (35.5% vs. 17.1%; p=0.014) and mechanical ventilator support (33.4% vs. 24.8%; p=0.028) needed were significantly higher compared to the non-geriatric cohort. Furthermore, major bleeding (22.7% vs. 11.4%) after receiving anticoagulation during admission, predominantly occurred among the geriatric cohort though this was statistically insignificant.

During the hospitalisation period, the prevalence rate of AKI (46.7% vs. 22.9%; p=0.004) and acute coronary syndrome

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

Characteristics	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Age in years, median (IQR)	59 (49.0-66.0)	69 (67.0-73.0)	54 (44.5-60.0)	**<0.001**[a]
Male Gender	91 (60.7)	26 (57.8)	65 (61.9)	0.635[b]
With at least one comorbidity	110 (73.3)	36 (80.0)	74 (70.5)	0.227[b]
Comorbidities				
Hypertension	78 (52.0)	28 (62.2)	50 (47.6)	0.101[b]
Diabetes mellitus	66 (44.0)	25 (55.6)	41 (39.0)	0.062[b]
Dyslipidaemia	25 (16.7)	11 (24.4)	14 (13.3)	0.094[b]
Ischemic heart disease	17 (11.3)	7 (15.6)	10 (9.5)	0.286[b]
Obesity	4 (2.7)	1 (2.2)	3 (2.9)	1.000[c]
End stage renal disease	4 (2.7)	0 (0.0)	4 (3.8)	0.317[c]
Chronic kidney disease excluding ESRF	3 (2.0)	1 (2.2)	2 (1.9)	1.000[c]
Alzheimer's disease	2 (1.3)	2 (4.4)	0 (0.0)	0.089[c]
Malignancy	1 (0.7)	0 (0.0)	1 (1.0)	1.000[c]
Other comorbid*	27 (18.0)	8 (17.8)	19 (18.1)	0.963[b]
Symptomatic at presentation	149 (99.3)	45 (100.0)	104 (99.0)	1.000[c]
Symptoms at presentation				
Cough	115 (76.7)	31 (68.9)	84 (80.0)	0.140[b]
Fever	106 (70.7)	24 (53.3)	82 (78.1)	**0.002**[b]
Shortness of breath	100 (66.7)	29 (64.4)	71 (67.6)	0.705[b]
Diarrhoea	49 (32.7)	8 (17.8)	41 (39.0)	**0.011**[b]
Loss of appetite	34 (22.7)	12 (26.7)	22 (21.0)	0.444[b]
Fatigue	31 (20.7)	16 (35.5)	15 (14.3)	**0.003**[b]
Sore throat	18 (12.0)	3 (6.7)	15 (14.3)	0.188[b]
Nausea/vomiting	18 (12.0)	2 (4.4)	16 (15.2)	0.062[b]
Chest pain/discomfort	15 (10.0)	2 (4.4)	13 (12.4)	0.233[c]
Arthralgia/myalgia	11 (7.3)	4 (8.9)	7 (6.7)	0.734[c]
Ageusia	7 (4.7)	3 (6.7)	4 (3.8)	0.429[c]
Anosmia	6 (4.0)	3 (6.7)	3 (2.9)	0.365[c]
Haemoptysis	1 (0.7)	0 (0.0)	1 (1.0)	1.000[c]
Other symptom[#]	41 (27.3)	13 (28.9)	28 (26.7)	0.780[b]
Temperature at presentation (°C), median (IQR)	38.0 (37.0-38.8)	37.5 (36.7-38.6)	38.1 (37.1-38.8)	0.054[a]
Day of illness at presentation, median (IQR)	5 (3.0-7.0)	4 (2.0-6.0)	6 (4.0-8.0)	**0.001**[a]
Category of illness at presentation				0.112[c]
2	5 (3.3)	3 (6.7)	2 (1.9)	
3	20 (13.3)	7 (15.6)	13 (12.3)	
4a	75 (50.0)	16 (35.5)	59 (56.2)	
4b	38 (25.4)	13 (28.9)	25 (23.8)	
5a	2 (1.3)	1 (2.2)	1 (1.0)	
5b	10 (6.7)	5 (11.1)	5 (4.8)	
Day of illness during CTPA, median (IQR)	10 (8.0-13.0)	9 (6.0-12.0)	10 (8.0-14.0)	**0.005**[a]
Category of illness during CTPA				0.261[c]
2	1 (0.7)	0 (0.0)	1 (1.0)	
3	2 (1.3)	0 (0.0)	2 (1.9)	
4a	56 (37.3)	18 (40.0)	38 (36.2)	
4b	34 (22.7)	6 (13.3)	28 (26.6)	
5a	30 (20.0)	9 (20.0)	21 (20.0)	
5b	27 (18.0)	12 (26.7)	15 (14.3)	
Treatment received during/prior to CTPA				
Inotropic support	23 (15.3)	11 (24.4)	12 (11.4)	**0.043**[b]
Systemic steroidal treatment	148 (98.7)	45 (100.0)	103 (98.1)	1.000[c]
Immunomodulators treatment	58 (38.7)	15 (33.4)	43 (41.0)	0.380[b]
Favipiravir treatment	111 (74.0)	34 (75.5)	77 (73.3)	0.776[b]
Anticoagulation regimen received within the last 48 hours prior to CTPA				0.121[c]
(a) Prophylactic low molecular weight heparin	108 (72.0)	37 (82.2)	71 (67.6)	
(b) Prophylactic unfractionated heparin	3 (2.0)	2 (4.4)	1 (1.0)	
(c) Therapeutic anticoagulation	31 (20.7)	5 (11.1)	26 (24.8)	
(d) Intermediate anticoagulation	2 (1.3)	0 (0.0)	2 (1.9)	
(e) None	6 (4.0)	1 (2.2)	5 (4.8)	
Haemodialysis during admission	10 (6.7)	2 (4.4)	8 (7.6)	0.724[c]
Inotropic support during admission	34 (22.7)	16 (35.5)	18 (17.1)	**0.014**[b]

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

Characteristics	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Highest oxygen support during admission				0.658[c]
No oxygen required	3 (2.0)	0 (0.0)	3 (2.9)	0.554[c]
Nasal prong	29 (19.3)	10 (22.2)	19 (18.1)	0.558[b]
Face mask	19 (12.7)	5 (11.1)	14 (13.3)	0.708[b]
Venturi mask 60%	9 (6.0)	1 (2.2)	8 (7.6)	0.280[c]
High flow mask	19 (12.7)	4 (8.9)	15 (14.3)	0.362[b]
High flow nasal cannula	30 (20.0)	10 (22.2)	20 (19.0)	0.656[b]
Mechanical ventilatory support (Intubated)	41 (27.3)	15 (33.4)	26 (24.8)	**0.028**[b]
Anticoagulation therapy received during admission	149 (99.3)	44 (97.8)	105 (100.0)	0.300[c]
Bleeding complication post anticoagulant				0.204[c]
Major bleeding[$]	22 (14.8)	10 (22.7)	12 (11.4)	
Minor bleeding[@]	5 (3.3)	1 (2.3)	4 (3.8)	
No bleeding complication	122 (81.9)	33 (75.0)	89 (84.8)	
Complications				
Acute transaminitis	82 (54.7)	26 (57.8)	56 (53.3)	0.616[b]
Acute kidney injury	45 (30.0)	21 (46.7)	24 (22.9)	**0.004**[b]
Acute coronary syndrome	5 (3.3)	4 (8.9)	1 (1.0)	**0.029**[c]
Acute stroke	2 (1.3)	2 (4.4)	0 (0.0)	0.089[c]
ICU admission	72 (48.0)	26 (57.8)	46 (43.8)	0.117[b]
Length of ICU stay, median (IQR)	8.0 (4.0-13.0)	7.5 (4.0-12.5)	8.5 (4.8-15.8)	0.235[a]
Length of hospital stay, median (IQR)	14.5 (11.0-20.0)	15.0 (12.0-19.5)	14.0 (10.5-20.0)	0.542[a]
Outcome				**0.001**[b]
Discharged	129 (86.0)	32 (71.1)	97 (92.4)	
In-hospital death	21 (14.0)	13 (28.9)	8 (7.6)	
Sixty-day all-cause mortality	22 (14.7)	14 (31.1)	8 (7.6)	**<0.001**[b]

IQR, Interquartile range
[a]Mann-Whitney U test
[b]Pearson Chi-square test
[c]Fisher's exact test
*Other comorbid: Chronic obstructive pulmonary disease, bronchial asthma, bronchitis, congestive cardiac failure, old cardiovascular accident, Parkinson disease, bipolar disorder, anaemia, hereditary spherocytosis, gastritis, fatty liver, benign prostate hypertrophy, gouty arthritis, obstructive sleep apnoea, hyperthyroidism, scleroderma, uterine fibroid, haemorrhoid, slipped disc, rheumatoid arthritis
[#]Other symptom: runny nose, chills and rigors, acid brash sensation, epigastric pain, orthopnea, parosxysmal nocturnal dyspnea, dizziness, heaviness over head, pre-syncopal attack, syncope, reduced consciousness, unconscious, diaphoresis, reduced urine output, left sided body weakness, alleged fall and slurred speech
[$]Major bleeding: Gastrointestinal bleed, occult bleed, or haematoma causing either (1) a fall in haemoglobin of 2g/dL or more, or (2) transfusion of 2 or more units of whole blood or red cells, or (3) fulfilling both criteria(1) and (2)
[@]Minor bleeding: Haematoma, epistaxis, haematuria, or occult bleed that does not fulfil the criteria for major bleeding

(8.9% vs. 1.0%; *p*=0.029) were significantly higher among the geriatric group. Noticeably, the prevalence rate of acute transaminitis was also remarkably high among both groups. Lastly, two cases of stroke (4.4%) were observed among the geriatric cohort.

Among the geriatric cohort, 57.8% (n=26) of them required ICU admission as opposed to 43.8% (n=46) among the non-geriatric cohort. Despite having shorter median of ICU stay among the former group, the median length of hospital stay was longer when compared to the non-geriatric group.

The in-hospital mortality rate (28.9% vs. 7.6%; *p*=0.001) was significantly higher among the geriatric cohort. As depicted in Figure 1, the cumulative probability of survival was significantly lower in geriatric cohort than non-geriatric cohort (68.9% vs. 92.4%; log rank, *p*<0.001). The mean survival time was 47.5 days in geriatric cohort and 58.1 days in non-geriatric cohort.

Comparison of laboratory data between the geriatric and non-geriatric cohorts

Analysis of the laboratory parameters showed that the median level of all full blood count parameters at admission was within normal range, except absolute lymphocyte count which was significantly lower among the geriatric cohort (median 0.9 × 10^9/L, IQR 0.6-1.3 vs. median 1.0 × 10^9/L, IQR 0.8-1.5; *p*=0.014). In addition, the geriatric cohort also demonstrated a significantly lower peak albumin (median 29g/L, IQR 26.0-32.0 vs. median 32 g/L, IQR 29.0-34.0; *p*=0.001) during admission. Both C-reactive protein (CRP) and ferritin levels were profoundly raised in both cohorts. Other laboratory results including peak AST, peak creatinine, peak procalcitonin and peak D-dimer levels were generally higher among the geriatric cohort. Overall, no significant differences were found between geriatric and non-geriatric cohorts, except serum absolute lymphocyte count at presentation and peak albumin level during admission (Table II).

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

Laboratory data	Normal range	Total (n=150)	Geriatric (n=45)	Non-Geriatric (n=105)	*p* value
Full blood count parameter at presentation, median (IQR)					
Hb (g/dL)	12.0-15.0	13.4 (12.6-14.7)	13.5 (12.7-14.6)	13.3 (12.5-14.9)	0.998[a]
WCC (x10^9/L)	4.0-10.0	6.9 (5.2-8.9)	6.8 (5.2-9.6)	6.9 (5.1-8.8)	0.884[a]
ALC (x10^9/L)	1.0-3.0	1.0 (0.8-1.4)	0.9 (0.6-1.3)	1.0 (0.8-1.5)	**0.014**[a]
Platelet (x10^9/L)	150-410	208 (165.0-267.3)	199 (163.5-238.0)	223 (168.0-275.0)	0.269[a]
Peak level throughout admission, median(IQR)					
Albumin (g/L)	34.0-50.0	31 (28.0-34.0)	29 (26.0-32.0)	32 (29.0-34.0)	**0.001**[a]
CRP (ng/L)	<5	124.1 (86.2-155.1)	137.0 (86.2-155.1)	122.9 (58.7-153.9)	0.164[a]
Ferritin (µg/L)*	10-291	1469 (688.0-2189.0)	1435.5 (688.0-2189.0)	1469.0 (197.5-1506.0)	0.746[a]
AST (U/L)	<34	73 (50.0-121.0)	76 (50.0-121.0)	71 (34.8-105.0)	0.311[a]
ALT (U/L)	10-49	92 (50.8-155.8)	77.5 (50.8-155.8)	97.0 (44.8-137.3)	0.691[a]
Creatinine (µmol/L)	44.2-97.2	97.1 (78.6-135.1)	108.9 (78.6-135.1)	95.5 (75.1-128.2)	0.240[a]
Procalcitonin (ng/ml)[#]	<0.05				0.627[b]
<0.05		14 (11.1)	3 (7.3)	11 (12.9)	
0.05-0.49		82 (65.1)	26 (63.4)	56 (65.9)	
0.50-2.00		19 (15.1)	8 (19.5)	11 (12.9)	
>2.00		11 (8.7)	4 (9.8)	7 (8.3)	
Peak level of D-dimer (µg/ml) pre-CTPA, n (%)	0.0-<0.5				0.319[b]
<0.5		7 (4.7)	0 (0.0)	7 (6.7)	
0.5-5.0		123 (82.0)	39 (86.6)	84 (80.0)	
5.1-20.0		12 (8.0)	3 (6.7)	9 (8.6)	
>20.0		8 (5.3)	3 (6.7)	5 (4.8)	

[a]Mann-Whitney U test
[b]Fisher's exact test
*Ferritin level was taken for 139 subjects (not taken for 11 subjects)
[#]Procalcitonin level was taken for 126 subjects (not taken for 24 subjects)

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

Radiological features	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Most proximal anatomical location				1.000[a]
Subsegmental	147 (98.0)	44 (97.8)	103 (98.1)	
Segmental	3 (2.0)	1 (2.2)	2 (1.9)	
Degree of involvement				0.369[a]
Single lobar, Unilateral	53 (35.3)	13 (28.9)	40 (38.1)	
Multilobar, Unilateral	2 (1.3)	0 (0.0)	2 (1.9)	
Multilobar, Bilateral	95 (63.3)	32 (71.1)	63 (60.0)	
COVID-19 pneumonia/Organising pneumonia changes				0.216[a]
Mild	48 (32.0)	13 (28.9)	35 (33.3)	
Minimal	6 (4.0)	0 (0.0)	6 (5.7)	
Moderate	56 (37.3)	16 (35.6)	40 (38.1)	
Severe	40 (26.7)	16 (35.6)	24 (22.9)	
Pulmonary angiopathy changes	50 (33.3)	23 (51.1)	27 (25.7)	**0.002**[b]
Other computerized tomography (CT) findings*	76 (50.7)	26 (57.8)	50 (47.6)	0.254[b]

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

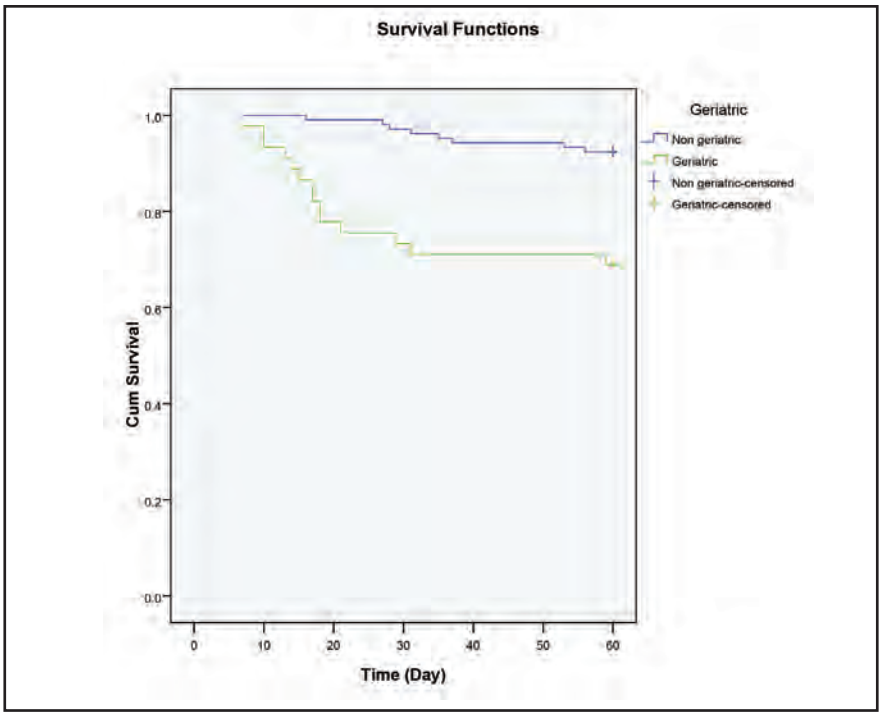

Fig. 1: Kaplan-Meier survival function curve for geriatric versus non-geriatric population

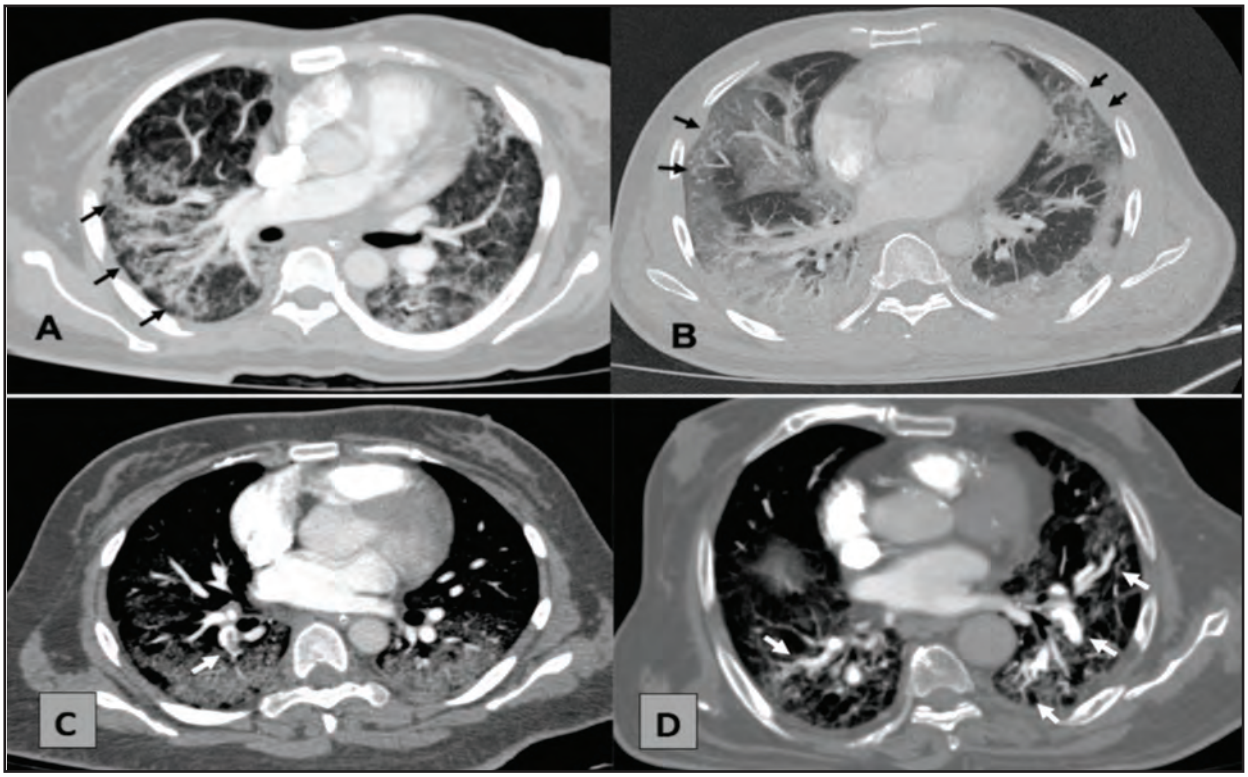

Fig. 2: Axial slice of CTPA demonstrates features of pulmonary angiopathy in two patients with severe COVID-19 pneumonia. (A) Image showed dilated branching and tortuous vessels in the right lower lobe (arrows). (B) There is a bilateral ground-glass opacification with consolidation and vascular tree-in-bud pattern distally, a sign of angiopathy (arrows). (C) CTPA of patient with COVID-19 pneumonia, day 10 after intubation demonstrates filling defects in right lower lobe pulmonary arteries (arrows). (D) CT of elderly patient at day 14 of illness showed dilated branching and tortuous vessels in both lower lobes representing features of pulmonary angiopathy

Comparison of Radiological Features Between the Geriatric and Non-geriatric Cohorts

Analysis of the CT features showed that the thrombotic lesions were primarily located in the peripheral pulmonary arteries with the most proximal anatomical location limited to the subsegmental and segmental arteries in both the geriatric and non-geriatric cohorts. The commonest pattern of PTE involvement was multilobar bilateral, followed by single lobar, unilateral and multilobar unilateral (Figure 2). It is noteworthy that severe degree of COVID-19 pneumonia or organising pneumonic changes were more common among the geriatric cohort, in contradistinction to mild, minimal and moderate changes which were more prevalent among the non-geriatric cohort. All these differences in radiological features were not statistically significant, except for the pulmonary angiopathy changes (51.1% vs. 25.7%; p=0.002) which was significantly higher among the geriatric cohort (Table III).

DISCUSSION

It is well established that the geriatric populations not only stand a greater risk of afflicting COVID-19 infection, but also report a poorer survival outcome due to a myriad of reasons. The foremost explanation for this observation has been well encapsulated under the moniker of immunosenescence or immunoparesis.[18,19] Fundamentally, it describes that due to the physiological ageing process, the host innate as well as cell mediated immune system have weakened, which consequently contribute to the poorer outcome when the hosts are incapable of mounting a robust immune response during infection. Also, the cardinal signs of typical COVID-19 infection, such as fever would be absent due to the blunted immune response.[20] Importantly, they are also having a heightened susceptibility towards thromboembolic complications which are known to be a negative survivor predictor.[12] Considering all these, identification of the common presenting symptoms among the elderly populations with PTE disease complicating COVID-19 infections are of paramount importance as it would enable a timely diagnosis.

In this report, we confirmed that PTE disease associated with COVID-19 infections could manifest in a wide array of symptoms which corroborate with the published literature.[21] It is noteworthy that a significant proportion our geriatric cohort were unable to mount a febrile response during presentation, which were in keeping with the-above-mentioned theory. Paradoxically, the increment in inflammatory markers was comparable to the non-geriatric cohort suggesting their intact ability in generating inflammatory proteins. This observation reaffirms the clinical usefulness of such biomarkers in denoting the hyperinflammatory phase during the clinical course of COVID-19 illness and allowing the clinicians to render the targeted treatment accordingly. Furthermore, atypical symptoms such as gastrointestinal symptoms were more likely to occur among the non-geriatric cohort, whilst neurological deficits only exclusively present among the geriatric cohort. In light of these findings, we recommend the clinicians to maintain a high index of suspicion of COVID-19 infection, especially among the geriatric population during the pandemic as their presenting symptoms could masquerade other common illnesses.[22,23]

There is a growing body of evidence to suggest that COVID-19 infection could trigger a systemic immune hyperactivation leading to cytokine storm that would culminate in a multi-systemic injury as well as hypercoagulable state. The later has been well elucidated under the appellation of immunothrombosis that underpins the pathophysiological process of PTE disease associated with COVID-19.[10,11] In our study, a significant portion of geriatric patients developed AKI and acute coronary syndrome which could be linked to cytokine storm induced by the viral infection. Notwithstanding, the incidence rate of acute transaminitis and acute stroke were equally notable. Though the later was not statistically significant, possibly due to being underpowered from the small event rates, this underscores the predisposition towards multi-organ involvement among the subjects with PTE disease associated with COVID-19.[24] Importantly, none of the subject had associated clinical lower limb deep vein thrombosis. Considering all these, extrapulmonary complications of COVID-19 infection should be actively monitored among hospitalised subjects, especially the elderly group.

It is universally agreed that timely thromboprophylaxis represents the quintessentially important strategy in preventing the development of PTE disease among the hospitalised patients with or without COVID-19 infection.[25,26] It is evident that almost all our subjects had been initiated on either thromboprophylaxis or therapeutic anticoagulations. Similarly, Valle et al and Leonard-Lorant et al reported the percentage of their PTE cases treated with thromboprophylaxis prior to CTPA examination were 83.1% (54/65) and 78.0% (25/32) respectively.[27,28] Nonetheless, a large prospective case control study would be needed to verify the net effects of thromboprophylactic treatment on the incidence of PTE disease associated with COVID-19 which has a distinctive pathophysiological pathway. In another note, recent data from Musoke et al, who reviewed anticoagulation and bleeding risk in patients with COVID-19, indicated that major bleeding regardless of site trends towards association with in-patient fatality (40.0% vs. 21.5%; p=0.054).[29] In this report, the incidence of major bleeding complications is appreciably higher among the elder group. Though it is not statistically significant, it serves to remind us about the judicious use of anticoagulant therapy after weighing in the bleeding risk, and caution against indiscriminate use of therapeutic anticoagulation without clear indication.

There were no discernible differences in regard to the radiological features between two groups, except the pulmonary angiopathy changes which predominantly occurred in the elderly cohort. As alluded earlier, in situ immunothrombosis is the principal cause of PTE disease associated with COVID-19 infection. This dysregulated inflammatory cascade contributes to widespread alveolar injury, disruption of pulmonary vascular endothelial cell thrombo-protective state and systemic coagulopathy. Ultimately, these would result in small vessel thrombi as well as pulmonary angiopathy. According to Yuan et al, the elderly COVID-19 cohort suffered from a more profound

hypercoagulable state as suggested by a significantly higher serum fibrinogen and D-dimer levels compared to the younger cohort.[30] In this report, the insignificant D-dimer levels and unavailability serum fibrinogen levels do not substantiate hypercoagulable state as the cause of pulmonary angiopathy in the elderly cohort. In fact, the hyperinflammatory phenomenon appears to be the more probable driver of pulmonary angiopathy observed among the later.

The unique thrombotic lesions which preferentially affect distal peripheral pulmonary artery branches with a preponderance of multilobar, bilateral involvement are generally in accordance with majority of the published studies. Several studies, for example Ooi et al and van Dam et al have unanimously reported that PTE disease correlate well with the degree of lungs parenchyma affected by COVID-19 pneumonia and our results concur with them.[31,32] Nonetheless, Amaqdouf et al has published a clinical vignette, depicting massive pulmonary embolism complicating mild COVID-19 pneumonia in a 92-year-old man who presented with acute respiratory failure.[33] Hence, our suggestions reflect the recommendations by Sathar et al whereby PTE disease should be suspected on COVID-19 individuals with rapid respiratory deterioration, unexplained tachycardia, haemodynamic instability or moderate to extensive COVID-19 pneumonic X-ray changes.[26]

Despite earlier presentation, the geriatric cohort demonstrated a significantly higher 60-day fatality rate. The clinical characteristic for mortality in our geriatric cohort, such as older age, critically ill, AKI and major bleeding complications were in keeping with the published literature.[29,34-37] Other plausible explanation for the adverse outcome is the immunosenescence phenomenon as alluded earlier. Lastly, significant hypoalbuminaemia and reduced absolute lymphocyte count could also plausibly contribute to a more severe COVID-19 disease and therefore poorer outcome among them.[38,39] In view of the inherently poorer survival outcomes, we recommend close collaboration with geriatrician in discussing the critical care of the elderly, especially pertaining to the resuscitation status as well as ethical consideration at time of pandemic.

We are cognizant of the several limitations in our study. Firstly, there was an unprecedented demand on CTPA examination requests during this study period which coincided with the peak of delta wave in 2021. Therefore, it is understandable that the actual prevalence rate of PTE disease among geriatric populations remained elusive under such circumstances, as those who were moribund or with do not resuscitate status would preclude CTPA examination due to perceived futility of care under such crisis. Also, frailty assessment which has been recognised as a survival predictor among the elderly population was not available due to the retrospective design of this study.[40] Lastly, we were unable to determine the interrater reliability or agreement as we only had single radiologist in this study, though this was not our study objective.

CONCLUSION

Overall, subtle differences in term of presenting symptoms exist between geriatric and non-geriatric patients. There were no major differences in the computerized tomography (CT) representation of both the thrombi distribution as well as the lung parenchyma affected with COVID-19 pneumonia, except the higher incidence of microangiopathic aberration among the elderly. The elderly patients were more susceptible to severe illness with consequent higher fatality outcomes. We recommend future researchers to conduct similar research among our post-vaccination population to further enrich our understanding towards pulmonary thromboembolic (PTE) disease associated with COVID-19.

ACKNOWLEDGEMENT

We acknowledge all the healthcare workers involved in the treatment of COVID-19 cases in Malaysia. Also, we would like to extend our gratitude towards Dr Ameen (Head of Geriatric Unit, HTAR) and Dr Eashwary (Head of Medical Department, HTAR) for their invaluable review of this paper. Lastly, we would like to thank Director General of Health Malaysia for his permission to publish this article.

ETHICAL APPROVAL

This study was registered with National Medical Research Register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). MREC Approval Letter: KKM/NIHSEC/P21-1451(12) NMRR ID: NMRR-21-1558-59028 (IIR)

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Management of patent foramen ovale in embolic stroke of undetermined source patients: Malaysian experts' consensus

Stephenie Ann Albart, MD[1], Abdul Hanif Khan Yusof Khan, MMed (Int Med)[2,3], Wan Asyraf Wan Zaidi, MMed (Int Med)[4], Annamalar Muthu Muthuppalaniappan, MRCP[5], Geetha Kandavello, MRCP (Paeds)[6], Koh Ghee Tiong, MRCPCH[7], Leong Ming Chern, MRCPCH[6], Liew Houng Bang, FRCP[8], Ong Beng Hooi, MRCP[9], Shanthi Viswanathan, MRCP[10], Hoo Fan Kee, MRCPS (Glasgow)[2,3], Irene Looi, FRCP[1,11], Yap Yee Guan, FRCP[12], Law Wan Chung, MRCP[13]

[1]Clinical Research Centre, Hospital Seberang Jaya, Ministry of Health Malaysia, Seberang Jaya, Pulau Pinang, Malaysia, [2]Department of Neurology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [3]Department of Neurology, Hospital Pengajar Universiti Putra Malaysia, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [4]Department of Medicine, Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, [5]Gleneagles Hospital Penang, George Town, Pulau Pinang, Malaysia, [6]Institut Jantung Negara, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, [7]Paediatric Cardiology Unit, Hospital Serdang, Kajang, Selangor, [8]Department of Cardiology, Hospital Queen Elizabeth II, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia, [9]Kedah Medical Centre, Alor Setar, Kedah, Malaysia, [10]Department of Neurology, Hospital Kuala Lumpur, Ministry of Health Malaysia, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, [11]Department of Medicine, Hospital Seberang Jaya, Ministry of Health Malaysia, Seberang Jaya, Pulau Pinang, Malaysia, [12]Sunway Medical Centre, Petaling Jaya, Selangor, Malaysia, [13]Department of Medicine, Hospital Umum Sarawak, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia

ABSTRACT

Introduction: About 20 to 40% of ischaemic stroke causes are cryptogenic. Embolic stroke of undetermined source (ESUS) is a subtype of cryptogenic stroke which is diagnosed based on specific criteria. Even though patent foramen ovale (PFO) is linked with the risk of stroke, it is found in about 25% of the general population, so it might be an innocent bystander. The best way to treat ESUS patients with PFO is still up for discussion.

Materials and Methods: Therefore, based on current evidence and expert opinion, Malaysian expert panels from various disciplines have gathered to discuss the management of ESUS patients with PFO. This consensus sought to educate Malaysian healthcare professionals to diagnose and manage PFO in ESUS patients based on local resources and facilities.

Results: Based on consensus, the Malaysian expert recommended PFO closure for embolic stroke patients who were younger than 60, had high RoPE scores and did not require long-term anticoagulation. However, the decision should be made after other mechanisms of stroke have been ruled out via thorough investigation and multidisciplinary evaluation. The PFO screening should be made using readily available imaging modalities, ideally contrast-transthoracic echocardiogram (c-TTE) or contrast-transcranial Doppler (c-TCD). The contrast-transesophageal echocardiogram (c-TEE) should be used for the confirmation of PFO diagnosis. The experts advised closing PFO as early as possible because there is limited evidence for late closure. For the post-closure follow-up management, dual antiplatelet therapy (DAPT) for one to three months, followed by single antiplatelet therapy (APT) for six months, is advised. Nonetheless, with joint care from a cardiologist and a neurologist, the multidisciplinary team will decide on the continuation of therapy.

KEYWORDS:
Patent foramen ovale, embolic stroke of undetermined source, cryptogenic stroke, PFO closure, stroke

INTRODUCTION

Stroke is one of the major causes of mortality and disability worldwide. In Malaysia, stroke is the third-leading cause of death and the second-leading cause of combined death and disability.[1] Based on the National Health and Morbidity Survey in 2006 and 2011, there was an increase in stroke prevalence from 0.3% to 0.7% among the Malaysian population.[2-4] From 2010 to 2014, the age-adjusted incidence and prevalence rates for ischaemic stroke almost tripled (34.2–96.2 per 100 000 and 42.8–118.7 per 100 000, respectively) in 5 years.[5] A steady increase in the incidence of ischaemic stroke by 29.5% annually was observed.[5] The Annual Report of the Malaysian Stroke Registry, 2009 to 2016, stated that 77% of stroke patients were between the ages of 50 and 79 years old, with the mean age of stroke onset being 62.5 years old.[6] Hypertension, smoking, diabetes and hyperlipidaemia were the common risk factors for first and recurrent ischaemic strokes identified among the Malaysian population.[5,7]

Ischaemic stroke is the most commonest type of stroke (79.4%), followed by haemorrhagic stroke (18.2%), transient ischaemic attack (2%) and strokes of unclassified causes

This article was accepted: 02 March 2023
Corresponding Author: Abdul Hanif Khan Yusof Khan
Email: ahanifkhan@upm.edu.my

(0.4%).[5] Based on pathophysiology, the causes of ischaemic stroke can be classified into large artery atherosclerosis (20%), small vessel occlusion (25%), cardio-embolism (20%), and other identified causes (5%).[8] About 20-40% of ischaemic stroke causes remain undetermined and are classified as cryptogenic stroke.[8] Cryptogenic stroke is further classified into three types: 1) multiple causes of stroke identified; 2) no causes identified due to insufficient diagnostic work-up; and 3) no causes identified despite extensive work-up.[9] Embolic stroke of undetermined stroke (ESUS) is a sub-type of cryptogenic stroke which is diagnosed based on specific criteria. The diagnostics criteria for ESUS are described in the later section. The classification of stroke and the potential causes of ESUS and other types of strokes are shown in Figure 1 which is generated based on Ntaios et al.[9] and Hart et al.[10] One of the possible causes of ESUS is patent foramen ovale (PFO).[10] PFO is the most common congenital cardiac abnormality in every 1 in 4 adults. The foramen ovale is a normal foetal heart structure that allows oxygenated placental blood to circulate from the right to the left atrium to reach the arterial circulation of the foetus. If the foramen ovale does not close naturally after birth during infancy, it is known as PFO.[11] The possible PFO-related stroke mechanisms are hypothesised as paradoxical embolism of a venous clot shunting through the PFO to the left atrium, in situ clot formation within the PFO, and atrial arrhythmias.[12]

There are a few treatment options available for secondary stroke prevention in ESUS patients with PFO, such as percutaneous transcatheter closure of PFO, antithrombotic therapy or a combination of both. Several clinical trials (CLOSURE, PC, RESPECT, CLOSE, REDUCE and DEFENSE-PFO trial) have been conducted to assess the efficacy and to compare the available treatments.[13-19] However, the outcomes of the trials were inconsistent due to the differences in study design and efficacy of the device used. The optimal management of ESUS patients with PFO is still being debated.

PFO is common in 25% of the general population. Even though it is associated with an increased risk of stroke, it could be just an innocent bystander. While we search for the best treatment option for ESUS patients with PFO, it is also crucial to consider whether treating such patients is beneficial and outweighs the potential risk. Therefore, Malaysian expert panels have gathered their thoughts and recommendations on managing ESUS patients with PFO based on the current evidence and their expert opinion on such patients. This consensus mainly aimed to educate the healthcare professionals involved in the management of acute ischaemic strokes regarding the diagnosis and management of PFO in ESUS patients based on the availability and feasibility of local resources and facilities in Malaysia.

MATERIALS AND METHODS

The Stroke Council of the Malaysian Society of Neurosciences (MSN) has scheduled three virtual meetings with neurologists, cardiologists, paediatric cardiologists, physicians and geriatricians from all regions of Malaysia: Central and South region in November 2021; North region in December 2021; and East Malaysia and the East Coast in January 2022. Each region was assigned to present and discuss a few specific related topics. Experts from the Kuala Lumpur and Selangor regions reviewed the selection of patients for PFO closure, while experts from the North Zone discussed the preferred screening and diagnostic technique for PFO, as well as the timing of PFO closure in ESUS. Experts from East Malaysia and the East Coast discussed post-PFO closure care and follow-up, medical treatment if PFO is not closed despite an indication for closure, and the strategies to raise awareness about PFO closure in ESUS. The experts' recommendations and suggestions from these three meetings were compiled into a Google form and emailed to all the experts for voting on the level of consensus. Table I shows the description of the level of consensus which was adapted from Diener et al.[20] Twenty-eight out of fifty-two experts responded to the Google form, representing a 53% response rate. The data were retrieved and analysed to determine the percentages of the level of agreement for each consensus statement. The findings were presented to a small group of experts (14 volunteers) from all regions at the last meeting, held in March 2022. Those statements that lacked majority support or contradicted other guidelines were re-discussed before reaching the final consensus. The final consensus among Malaysian experts is presented in this article. The co-authors reviewed and commented on the first draft of the manuscript in June 2022. Subsequently, the draft was revised accordingly until no further comments were received from all the co-authors. The final draft was sent to experts listed in Appendix A from the Malaysian PFO-Stroke Working Group for review, and it was finalised in September 2022.

PREFERRED SCREENING AND DIAGNOSTIC STRATEGY

Diagnostic strategy for ESUS

A thorough investigation should be conducted to rule out any additional potential causes of the suspected ESUS before considering PFO closure.[21]

Hart et al. (10) suggested the diagnostic criteria for ESUS and the minimum diagnostic assessment that should be done.[10] These are shown in Table II.

First of all, clinicians should get brain imaging from patients whose PFO closure is being investigated to confirm the size and distribution of the strokes and to look for embolic patterns or lacunar infarcts (which often involve a single deep perforator with a diameter of less than 1.5 cm).[21]

Occult atrial fibrillation (AF) is important in cryptogenic stroke as it is often asymptomatic and must be ruled out before considering PFO closure. A few screening methods are available to detect AF, such as 12-lead ECG, 24 to 48-hour Holter monitor, external event monitor, single-lead ECGs, in-patient cardiac telemetry and invasive methods such as implantable loop recorder.[22] Even though prolonged cardiac monitoring might not be easy to get in some hospitals, at least a baseline ECG should be done to rule out persistent AF.[21,23] However, comprehensive cardiac monitoring is advised whenever possible because studies have shown that it increases the likelihood of detecting AF.[24-27] The best monitoring approach and duration are yet to be determined and can be based on effectiveness, cost and patient preference.[28] Some experts suggested continuous cardiac monitoring for at least 24 hours for AF detection.[9,29] For

Table I: Description of the level of consensus

Consensus Level	Explanation
Should do this	Consensus to support a specific approach, treatment, or position
May do this	Limited evidence, and mixed opinions. Sufficient confidence and no contradictions regarding supported approach, treatment, or position
Should not do this	Consensus to discourage a specific approach, treatment, or position
Unsure	Insufficient data/experience, too many mixed opinions. Additional clinical evidence is required

Adapted from Diener et al. [20]

Table II: Diagnostic criteria and recommended work-up for ESUS

ESUS Criteria	Recommended Work-up
■ Stroke detected by CT or MRI that is not lacunar	• Brain CT or MRI [Lacunar is defined as a subcortical infarct smaller than or equal to 1·5 cm (≤2·0 cm on MRI diffusion images) in the largest dimension.]
■ The absence of extracranial or intracranial atherosclerosis causes ≥50% luminal stenosis in arteries supplying the area of ischaemia	• Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)
■ No major-risk cardioembolic source of embolism*	• 12-lead ECG • Precordial echocardiography • Prolonged cardiac monitoring with automated rhythm detection
■ No other specific cause of the stroke was identified*	

*Please refer to the examples of the major risk cardioembolic sources of embolism and other causes of stroke in Fig.1

Table III: The advantages, limitations, sensitivity (Sn), and specificity (Sp) of different modalities for PFO detection

Imaging Modalities	Advantages	Limitation	Weighted Mean Sn and Sp
Contrast transcranial Doppler (c-TCD)	• Non-invasive • Cost-effective • Can perform at the bedside • Can repeat at different body positions • Able to detect small shunts • Easy availability	• Unable to distinguish intracardiac and intrapulmonary shunts • Unable to visualise cardiac structures	Sn: 97% Sp: 93%
Contrast transthoracic echocardiogram (c-TTE)	• Non-invasive • Able to visualise cardiac structures • Easily available	• Limitations in discriminating against a small amount of RLS	Sn: 46% Sp: 99%
Contrast transesophageal echocardiogram (c-TEE)	• Able to visualise precise anatomy of PFO • Able to discriminate PFO shunt from intrapulmonary shunt	• Semi-invasive • Valsalva manoeuvre may be difficult to perform due to sedation • Limitations in discriminating against a small amount of RLS	Sn: 89.2% Sp: 91.4%

individuals who are older than 40 and have a high risk for AF, prolonged monitoring for AF detection for at least 28 days may be an option.[9,21] High risks for atrial fibrillation include hypertension, obesity, sleep apnoea, an enlarged left atrium, elevated NT-proBNP, frequent premature atrial contractions, increased P-wave dispersion, a prolonged PR interval, multi-territorial infarcts, etc.

Complete vascular imaging (Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)) of the cervical and intracranial vessels should be obtained to look for dissection, vasculopathy and atherosclerosis.[21]

If the hypercoagulable condition is suspected, a complete blood count (haemoglobin and platelet count), factor V Leiden, protein C, protein S, antithrombin III, homocysteine levels, prothrombin G20210A mutation and antiphospholipid antibodies test can be done.[30] Brain and pelvic Magnetic Resonance Venography (MRV) are recommended to look for cerebral venous sinus thrombosis and May–Thurner syndrome, respectively.[30]

PFO Detection

PFO does not increase the risk of early stroke recurrence in ESUS patients.[31] However, the risk of recurrent stroke is generally high in the first few weeks after a stroke. Therefore, Asian-Pacific experts suggested that recent ESUS patients should be given higher priority for PFO screening, which may be done within 2 weeks of stroke.[20]

PFO can be diagnosed based on the direct or indirect visualisation of right-to-left shunting (RLS). A bubble contrast transthoracic echocardiogram (c-TTE), contrast

Table IV: Preferred screening and diagnostic strategy

No	Statements	Consensus Level
	Diagnostic Strategy For ESUS	
1.	In patients being considered for PFO closure, perform a thorough evaluation to rule out alternative mechanisms of stroke.	Should do this
2.	In patients being considered for PFO closure, confirm stroke size and distribution, and assess for an embolic pattern or a lacunar infarct via brain imaging (MRI or CT).	Should do this
3.	In patients being considered for PFO closure, obtain complete vascular imaging (MRA or CTA) of the cervical and intracranial vessels to look for dissection, vasculopathy, and atherosclerosis.	Should do this
4.	In patients considered for PFO closure, perform a baseline ECG to look for atrial fibrillation.	Should do this
5.	In patients being considered for PFO closure, prolonged cardiac monitoring should be considered if there is a risk of atrial fibrillation.	May do this
	PFO Detection	
6.	Highest priority: ensure that patients with recent ESUS are screened for PFO.	Should do this
7.	For PFO screening, use bubble contrast transthoracic echocardiography (c-TTE) or bubble contrast transcranial Doppler ultrasound (c-TCD) with and without Valsalva manoeuver to assess for a right-to-left shunt and determine the degree of shunting.	Should do this
8.	Use contrast transesophageal echocardiography (c-TEE) for confirmation of PFO.	May do this
9.	Use the imaging modalities that are readily available in the hospital and on which the technical staff is best trained and most experienced (c-TTE, c-TCD, c-TEE, intracardiac echocardiography).	Should do this
10.	Ensure echocardiography is performed for imaging other cardiac structures to explore other sources of cardioembolic stroke.	Should do this
11.	Echocardiography is to be performed within two weeks after the stroke, depending on the local availability of services.	May do this

Table V: RoPE Score

Patient Characteristic	Points
No history of hypertension	+1
No history of diabetes mellitus	+1
No history of TIA or stroke	+1
Non-smoker	+1
Cortical infarct on imaging	+1
Age (y)	
18 to 29	+5
30 to 39	+4
40 to 49	+3
50 to 59	+2
60 to 69	+1
>70	+0
Total RoPE score	0-10

Adapted from Kent et al.[43]

Table VI: Patent Foramen Ovale - Associated Stroke Causal Likelihood (PASCAL) classification

PFO-related stroke	Low RoPE Score (≤6)	High RoPE Score (>6)
High-risk PFO (e.g Large shunt PFO and/or ASA)	Possible	Probable
Low-risk PFO (e.g Small shunt without ASA)	Unlikely	Possible

Adapted from Kent et al.[49]

transesophageal echocardiogram (c-TEE), and contrast transcranial Doppler (c-TCD) are the methods used to detect shunting from a PFO. TEE is the gold-standard method for detecting PFO. A bubble study is often performed together with an echocardiogram or a transcranial Doppler study (TCD) to assess the RLS when a PFO is suspected. In this study, the microbubbles (agitated saline or gaseous contrast agent) are injected into the peripheral vein. The patient is asked to perform a Valsalva manoeuvre to raise the pressure on the right side of the heart. The appearance of bubbles in the left atrium within three cardiac cycles during the echocardiogram confirms the presence of a shunt. Whereas the appearance of at least one bubble in the middle cerebral artery within 40 seconds of agitated saline injection during the TCD confirms the presence of shunting.[30] (Note that late bubble arrival is also associated with extra-cardiac shunts)

A meta-analysis comparing c-TCD versus c-TTE showed that c-TCD is reliable in ruling out PFO, whereas c-TTE is reliable in diagnosing PFO. Contrast TCD appeared to have a higher overall diagnostic yield than c-TTE. In fact, contrast TCD (c-TCD) is more sensitive to RLS detection than contrast TTE (c-TTE) or contrast TEE (c-TEE). It is suitable for use as an initial screening approach for RLS.[23,32-34] Nevertheless, this does not

Table VII: Patient selection for PFO closure

No	Statements	Consensus Level
1.	PFO closure in patients younger than 60 with an embolic-appearing infarct with no other mechanism of stroke was identified.	May do this
2.	PFO closure in patients with RoPE score >6.*	Should do this
3.	PFO closure in patients with RoPE score ≤6 is on a case-by-case basis where no other attributable causes for the cryptogenic stroke are identified and where the benefit outweighs the immediate and long-term risk.*	May do this
4.	PFO closure in patients with a lacunar stroke by imaging (single, small, deep infarct (infarct size <1.5cm)).	Insufficient data
5.	PFO closure in younger patients (e.g., <30 years) with a lacunar stroke (single, small, deep infarct (infarct size <1.5cm)), a large shunt, and absence of any vascular risk factors.	May do this / Insufficient data
6.	PFO closure in patients with a large PFO shunt (defined by the passage of > 20 microbubbles or maximum separation of septum of ≥2mm).*	May do this
7.	PFO closure in patients with an atrial septal aneurysm.*	May do this
	PFO in Patients Aged More Than 60 Years	
8.	PFO closure in patients over 60 years of age who are in biologically good condition and with strong indications of PFO causality in the embolic stroke mechanism, e.g., significant right-to-left shunt, atrial septal aneurysm.	May do this / Insufficient data
9.	PFO closure in patients over 60 years of age without high-risk PFO.	Should not do this
	PFO Closure in Patient Requiring Oral Anticoagulant (OAC)	
10.	PFO closure in patients with evidence of thrombi/ emboli and requirement for prolonged but not indefinite OAC (likely to be related to deep venous thrombosis).	May do this
11.	PFO closure in patients with an unrelated requirement for indefinite OAC.	Should not do this
	Multidisciplinary Approach	
12.	Before undergoing PFO closure, clinicians with expertise in stroke assess patients and ensure that the PFO is the most plausible mechanism of stroke.	Should do this
13.	Before undergoing PFO closure, clinician with expertise in assessing the degree of shunting and anatomical features of a PFO, and performing PFO closure, to assess whether the PFO is anatomically appropriate for closure, to ascertain whether other factors are present that could modify the risk of the procedure, and to address post procedural management.	Should do this
14.	In a patient for whom PFO closure is being considered, a shared decision-making approach between clinicians and the patient is to be used.	Should do this
15.	Comply with indications for PFO closure according to international/global guidelines/consensus statements.	Should do this

*Note that PASCAL classification can be considered for patient selection for PFO closure.

Table VIII: Timing of PFO closure in ESUS

No	Statements	Consensus Level
1.	ESUS with evidence of significant PFO: Close as early as possible.	Should do this
2.	Late (> 1 year) PFO closure in ESUS patients with evidence of significant PFO and no additional risk factors developed since the stroke.	May do this

Table IX: Post-PFO closure treatment and follow-up

No	Statements	Consensus Level
1.	Dual antiplatelet therapy (DAPT) for one to three months, followed by single APT for six months. The decision on continued therapy is to be made by the multidisciplinary team.	Should do this
2.	Echocardiography to assess erosion and other major devices-, procedures-, or cardiac-related complications when there is a high index of suspicion.	Should do this
3.	Follow-up by echocardiography every three months depending on the resources (in case of a residual shunt to inform the decision on DAPT)	May do this
4.	Monitoring of patients is based on the remnant risk of stroke, and the frequency is based on patients' needs and local resources. For centers that do not have resources to monitor and quantify residual shunt, patients should be referred to the appropriate clinicians with expertise and resources.	Should do this
5.	In the event of a rare residual shunt after PFO closure, the subsequent management is to be individualised with the team approach to weighing the options of the repeat procedure and/or antiplatelet regimes based on the patient's overall risk assessment. Such patients are on lifelong follow-up because risk assessment is dynamic as age increases and other comorbidities may develop in the future.	May do this
6.	In case of recurrent ischemic stroke: explore any secondary cause and confirm (non-) compliance to antithrombotic therapy.	Should do this

Table X: Medical therapy if the PFO is not closed despite an indication for closure

No	Statements	Consensus Level
1.	In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend either an antiplatelet medication such as aspirin or anticoagulation (using a vitamin K antagonist, a direct thrombin inhibitor, or a factor Xa inhibitor).	May do this

Table XI: Creating awareness about PFO closure in ESUS

No	Statements	Consensus Level
1.	Industry's role: continue supporting training and education programmes at general neurology meetings and events.	Should do this
2.	Set up online training and national forums.	Should do this
3.	Conferences: create awareness and organise screening training for technicians.	Should do this
4.	Hospital CMEs	Should do this

preclude echocardiography to rule out cardio-embolism mechanisms and confirm the presence of an intracardiac shunt, of which c-TCD is unable to differentiate.[20,21,24] Contrast TTE, however, showed limitations in diagnosing PFO with the small or delayed shunt.[35] Therefore, HSC/HSO experts suggested that c-TCD and/or c-TTE should be used for initial screening of RLS to diagnose PFO.[9] AAN also emphasised using bubble contrast, with and without Valsalva manoeuvre to assess for RLS and grade the shunting.[21] Test sensitivity was shown to improve with the Valsalva manoeuvre.[36] It is unlikely to be a high-risk PFO if there is minimal or no shunt on c-TCD after the Valsalva manoeuvre.[37] As TEE is particularly helpful in establishing the anatomy of the PFO and its adjacent structures, it continues to be the gold standard for PFO diagnosis.[28]

Each modality has its advantages and limitations.[32] These are listed in Table III along with the sensitivity and specificity of different modalities for RLS and PFO detection.[38-40]

HSC/HSO experts advised that a skilled operator conduct a c-TEE for PFO detection and PFO closure assessment.[9] Some modalities are not widely available in all acute stroke settings, especially in Malaysia. Asian-Pacific experts suggested using the best available modalities that the operator is trained in and most experienced in.[20]

The consensus among Malaysian expert panels regarding the preferred screening and diagnostic strategy has been summarised in Table IV.

PATIENTS SELECTION FOR PFO CLOSURE

To answer which patients can benefit from PFO closure, we need to carefully evaluate the inclusion criteria of the clinical trials that demonstrated the superiority or efficacy of PFO closure over the control groups.

In the earlier randomised control trials published in 2012 (CLOSURE) and 2013 (PC and RESPECT), PFO closure failed to show a significant reduction in stroke recurrence compared to antithrombotic medication alone in a cryptogenic stroke patient with PFO less than 60 years old.[13,14,17] The main reasons for the trial failure were probably due to the lack of high-risk PFO patient inclusion, unclear methods of confirmation of cryptogenic stroke, and a short follow-up period for a low annual risk of recurrent stroke among the study population.[41] Subsequently, from 2017 onwards, trials that included high-risk PFO patients (CLOSE, REDUCE, and DEFENSE-PFO trials) or prolonged the follow-up period (RESPECT follow-up trial), showed a significant reduction in stroke recurrence among the patients who had undergone PFO closure compared with the medical therapy group.[15,16,18,19] The DEFENSE-PFO is the only trial that recruited subjects above 60 years old; the others were mostly below 60 years old. Thus, the trial outcome might not be generalised for all.

Approximately 50% of all young patients with ischaemic stroke have a PFO.[42] PFO is more common in younger cryptogenic stroke patients and is more likely to be pathogenic than in older patients.[34] The European Society of Cardiology (ESC) stated that when the patients are young and have no other risk factors, PFO is more likely to be pathogenic.[23] The guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and the American Academy of Neurology (AAN) recommended PFO closure in patients younger than 60 years with an embolic-appearing infarct and no other mechanism of stroke identified.[21,24] AAN additionally mentioned that such recommendation may be following a discussion of the potential benefits of reducing stroke recurrence and the risks of complications from the procedures.[21]

The Risk of Paradoxical Embolism (RoPE) scores can also be considered before deciding on PFO closure. The RoPE score is an assessment tool to determine the probability that a PFO is related to a cryptogenic stroke.[43] Table V shows the scoring for the RoPE score. A higher score indicates a higher probability that a PFO is associated with a cryptogenic stroke. A score of above 7 indicates a causative risk of above 72%. However, the risk of recurrent stroke decreases with increasing RoPE scores. The estimated 2-year stroke/TIA recurrence rates decreased from 20% in the lowest RoPE score to 2% in the highest. Therefore, it cannot be solely used to determine which individuals with PFO-related strokes may benefit from closure. The RoPE score does not consider the PFO's high-risk anatomic or physiological aspects and should be used in conjunction with other factors.[34]

Kuijpers et al. (44) suggested the closure of a PFO in cryptogenic stroke patients with a RoPE score of more than eight and at least one clinical risk factor.[44] The Asian-Pacific region experts stated that PFO closure should be considered in patients with a RoPE score of six or more and may be

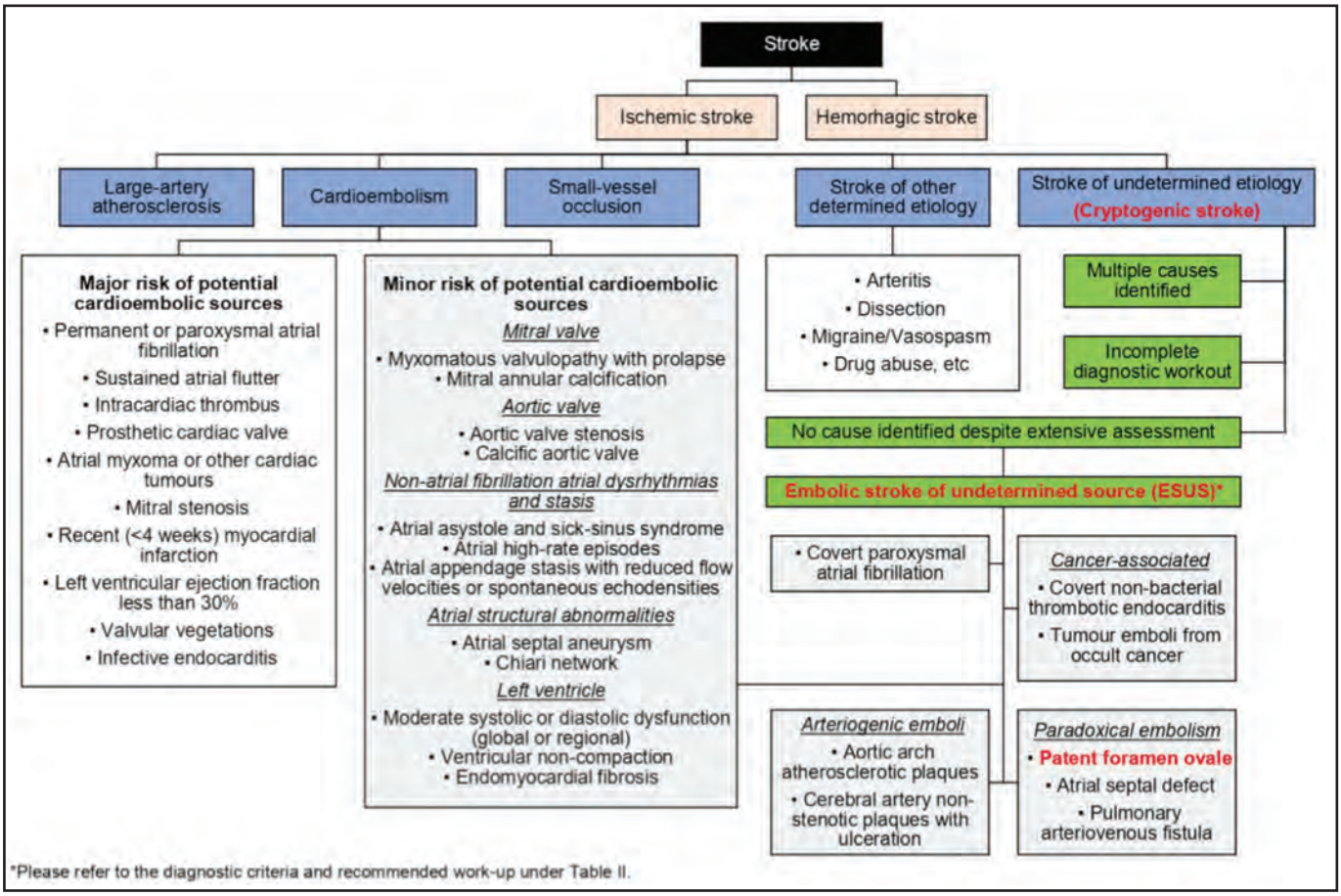

Fig. 1: Classification of stroke and the potential causes of ESUS

considered in patients with a score of less than six.[20] The recent review by Elzanaty et al. (45) mentioned that in patients aged 60 or younger with recent cryptogenic stroke with PFO, guideline recommendations consider the need for PFO closure on a case-by-case basis and individual risk factors.[45]

Cortical infarction is mostly due to embolism, but it is still possible that the subcortical infarct or lacunar stroke can be embolic.[23] Lacunar infarcts are a subtype of ischaemic stroke that occurs in small, deep-penetrating arteries of the brain. Up to 25% of all ischaemic strokes are due to a lacunar infarct.[46] Since lacunar strokes are unlikely due to a distant embolic source, PFO closure may be appropriate in young patients with a lacunar stroke plus a PFO if other risk factors for cerebral small vessel disease and atrial fibrillation (AF) have been ruled out.[46] However, the Asian-Pacific experts do not recommend PFO closure in a lacunar stroke.[20] Moreover, lacunar stroke was one of the trial exclusion criteria.[15,19] According to AAN, PFO closure, however, may be recommended for younger patients (e.g., 30 years old) with a single, small, deep stroke (1.5 cm) with the presence of a large shunt and no vascular risk factors that would lead to intrinsic small-vessel diseases, such as hypertension, diabetes or hyperlipidaemia.[21]

As mentioned earlier, trials that included high-risk PFO patients showed a favourable outcome with PFO closure. High-risk PFO is defined as PFO with atrial septal aneurysm (ASA), a condition characterised by hypermobility of the inter-atrial septum (phasic septal excursion into either atrium ≥10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥2 mm.[15] Besides that, a prominent Eustachian valve and large (≥20 microbubbles) right-to-left shunt were also anatomical characteristics of high-risk PFO.[42] The European Society of Cardiology (ESC) stated that ASA and PFO size are linked to the association between PFO and cryptogenic stroke.[23] The presence of ASA was related to stroke recurrence in PFO-associated stroke patients but not in large PFO patients.[47] In contrast, AAN suggested that patients with a large shunt may benefit from PFO closure, but ASA without a large PFO is questionable.[21] In a recent review, PFO patients with ASA likely have a stronger link to the risk of recurrent stroke.[48] A large PFO and ASA do not necessarily indicate a significant risk factor for a recurrent stroke, but they may indicate that the PFO is likely very pathogenic and may benefit from closure.[34] Patients with a RoPE score ≥7 with high-risk PFO may be good candidates for PFO closure.[26]

The Patent Foramen Ovale - Associated Stroke Causal Likelihood (PASCAL) classification system combines RoPE score and PFO features to assess patients who will benefit from PFO closure to prevent recurrent stroke.[49] As shown in Table VI, PASCAL classifies patients into three categories based on their causal relatedness: unlikely, possible, and probable.

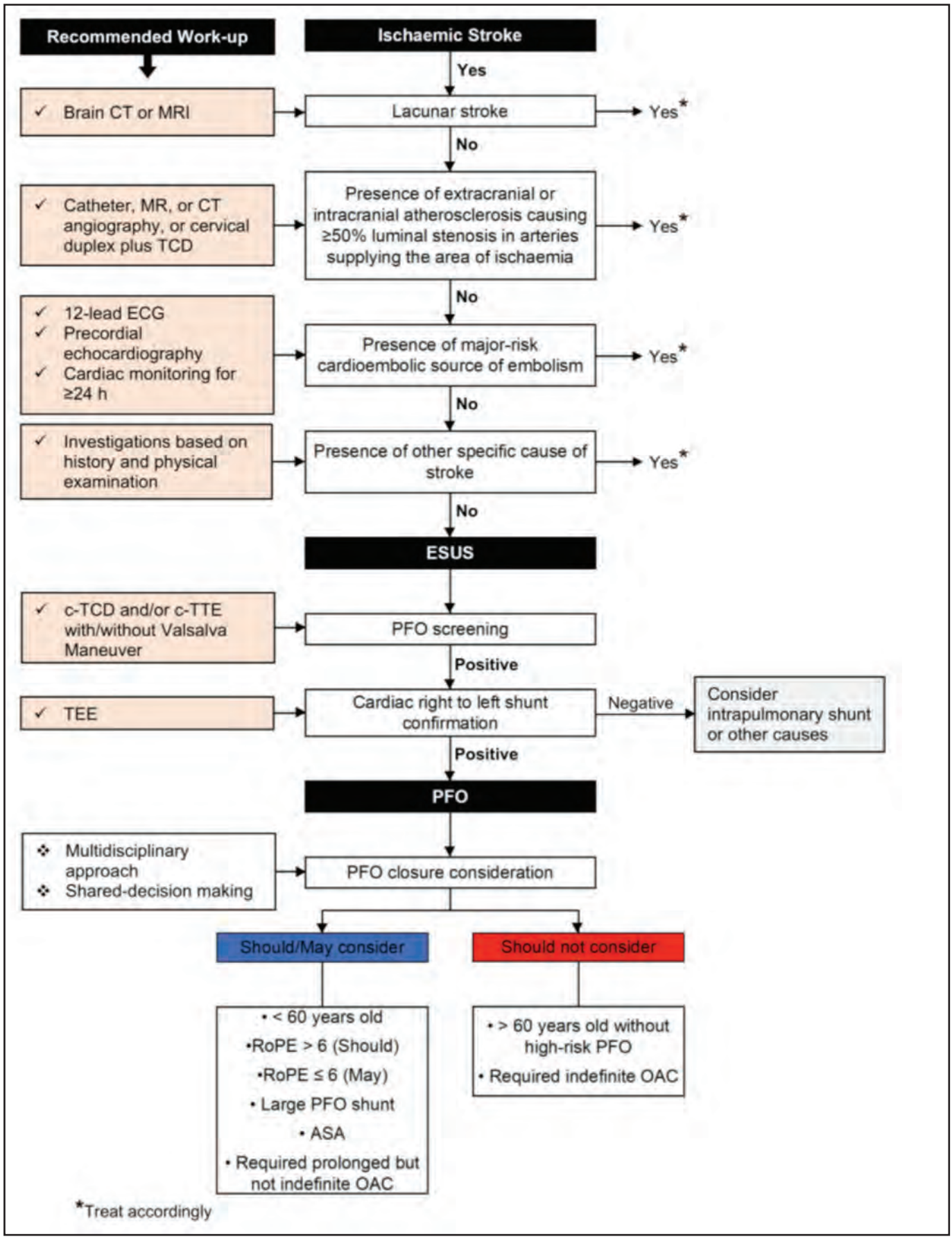

Fig. 2: Diagnostic approaches of PFO in cryptogenic stroke

About 15% of patients in the PASCAL "unlikely" classification without high-risk PFOs and vascular risk factors, did not benefit from PFO closure. However, 90% relative risk reduction was noted for PASCAL "probable" patients with high-risk PFO and a high RoPE score after PFO closure.[49] Therefore, the PASCAL classification system should guide clinicians during the individualised decision-making for PFO closure patient selection.

PFO Closure in Patients More Than 60 Years

More randomised trials to assess the safety and efficacy of PFO closure in people over 60 years old are needed to provide recommendations for these. For patients over 60 years of age, Asian-Pacific experts suggested that PFO closure may be suitable if they are in biologically good condition and have strong indications of PFO causality in the embolic stroke mechanism, e.g., significant right-to-left shunt and ASA.[20] The ANN and Thaler et al. (50) suggested we may offer PFO closure if they have very limited vascular risk factors and thorough evaluation has ruled out other mechanisms of stroke, including AF.[21,50] Even though elderly patients are more prone to additional stroke risks and may be excluded for PFO closure, they may still be at risk of venous thromboembolism and right-to-left shunt in the presence of a PFO.[26] However, the benefit of PFO closure in elderly patients, especially those with competing stroke mechanisms, is still unknown.

The risk of stroke in PFO patients is much higher in the older age group.[51] However, the risk of adverse events during PFO closure is also considerably higher (10.9%) in this age group.[52] The expert panellists from the Hellenic Stroke Organisation and the Working Group for Stroke of the Hellenic Society of Cardiology (HSO/HSC) are against the PFO closure in extreme age groups (<18 and >60 years) and may be considered on a case-by-case basis following a thorough examination.[9] According to Asian-Pacific expert panels, PFO closure should not be performed in patients over 60 who do not have a high-risk PFO.[20] It should not be inferred that PFO closure will benefit older patients with high-risk PFO because a prior study found that stroke recurrence rates in high-risk PFO patients > 60 years who underwent PFO closure were not significantly different from those who received medical therapy alone.[53]

PFO Closure in Patient Requiring Oral Anticoagulant (OAC)

Some patients may be on long-term oral anticoagulation (OAC) due to suspected or confirmed hypercoagulabilities such as thrombophilia, unprovoked deep venous thrombosis, or unprovoked pulmonary embolism. If a stroke patient with PFO with such a condition is considered for PFO closure, the clinician should inform the patient that the benefit of PFO closure in conjunction with anticoagulation is uncertain.[21,34] The Asian-Pacific expert panels suggested that PFO closure may be considered in patients with evidence of thrombi or emboli and a need for prolonged but not indefinite OAC, such as those with deep venous thrombosis.[20] However, PFO closure should not be performed in patients who have comorbidities that requires an indefinite OAC since it is likely to cause more harm than benefit, in addition to the danger of OAC-related bleeding.[20]

Multidisciplinary Approach

During the decision-making process for PFO closure, the probability of the PFO being a cause for ESUS and the risk of recurrence of a person must be considered.[23] PFO features need to be assessed before deciding on PFO closure.[23] A trained, experienced clinician should evaluate the degree of shunting and anatomic aspects of a PFO and whether it is suitable for closure. Clinicians should also ensure no additional factors may affect the procedure's risk and should be competent to handle the post-closure management.[21]

Shared decision-making is an integral part of patient-centered care. Clinicians should explain the available treatment options, provide risk, and benefit information, understand their concerns, and assist them in making decisions. The decision for PFO closure or medical therapy in ESUS patients with a PFO should be made jointly by the patient, a neurologist, and a cardiologist.[9,24,34,54]

Indications for PFO closure should be in accordance with the updated international guidelines and consensus statements.[20] The consensus among Malaysian expert panels regarding the patient selection for PFO closure has been summarised in Table VII. (*Note that PASCAL classification can be considered during patient selection for PFO closure.)

Figure 2 illustrates the Malaysian experts' suggested diagnostic approaches of PFO in ESUS.

TIMING OF PFO CLOSURE IN ESUS

Experts from the Asian-Pacific region suggested that ESUS with evidence of significant PFO should be closed as soon as possible.[20] However, no duration was specifically mentioned. In addition, they suggested that late PFO closure (> 1 year) may be performed in ESUS patients with evidence of high-risk PFO and no new risk factors since the stroke.[20] However, there is no evidence from clinical trials to support this recommendation. Most of the clinical trials that supported PFO closure included patients who had a recent stroke within 6 or 9 months.[15,16,18,19] The French Neurovascular Society and the French Society of Cardiology (FNS/FSC) have recommended PFO closure in patients with recent (≤ 6 months) ischaemic stroke. However, this time frame can be extended if AF detection is required for a longer duration.[55]

The consensus among Malaysian expert panels regarding the timing of PFO closure in ESUS has been summarised in Table VIII.

POST-CLOSURE TREATMENT AND FOLLOW-UP

No procedure is risk-free, and PFO closure is no exception; not only is it invasive, but PFO closure may also be accompanied by complications such as thrombus formation on the device and the development of AF following the procedure.

PFO closure device implantation increased thromboembolism risk by 1-2%.[41] In addition, the risk of AF was substantially higher in PFO closure than in medical therapy, ranging from 2.9% to 6.6%, based on the previous clinical trial data.[50] According to a meta-analysis of AF rates

after PFO closure, AF developed in 3.7 patients per 100 patient-years of follow-up. The risk of AF was greatest in the first 45 days after the procedure, and PFO closure increased the odds of having AF by 5.3 times over medical therapy.[56] Therefore, it is appropriate to administer dual antiplatelet therapy (DAPT) after PFO closure. Furthermore, PFO closure with medical therapy has been considered more cost-effective than medical therapy alone.[45]

Although no data supported the optimal DAPT duration, most guidelines and consensus recommended DAPT for up to 6 months, followed by a single antiplatelet agent.[9,23,41] Experts from FNS/FSC and the Asian-Pacific region suggested DAPT for up to 3 months, followed by a single APT.[20,55] Uncertainty remains on the length of time that a single APT should be continued. Still, some suggest that it may be continued for up to 5 years.[23,41,55] However, the decision to continue APT should be made by an expert clinician, such as a neurologist, based on the overall risks and benefits for the patient.[20,23] Low-dose aspirin and clopidogrel were the common choices of APT.[9,55]

Other long-term complications that may occur after PFO closure include the presence of residual shunt, scar tissue development, endocarditis, pericardial effusion, and the risk of aortic root dilation and erosion.[41,45] About 2.6% of patients may develop uncommon long-term complications following PFO closure.[23] If complications are suspected, imaging such as echocardiography should be performed.[20,55]

There were no clear guidelines for the timing and frequency of follow-up evaluations following the PFO closure. About 19.5% of post-closure patients had residual shunt at four months, which dropped to 8.4% at 11 months and 2.8% with a persistent mild shunt at two years during follow-up.[57] The ESC suggested c-TCD after six months post-closure to assess for the residual shunt and annually in the presence of a residual shunt.[23] FNS/FSC experts recommended 12-lead ECG and c-TTE at 1 and 12 months.[55] Asian-Pacific experts recommended more frequent imaging follow-ups every three months and advised re-evaluating the DAPT decision if a residual shunt was seen.[20] Long-term antithrombotic medication should be considered after discussion with cardiologists and neurologists for people with residual shunt who are at risk for recurrent stroke. In the event of a recurrent stroke, the patient's compliance with antithrombotic treatment must be verified, and additional causes must be investigated.[20]

The meta-analysis of AF following PFO closure revealed that older patients have a considerably increased risk of developing AF after closure.[56] Higher risk groups were hence justifiable for more regular follow-up.[20] CHA_2DS_2-VASc score can be used to determine the higher-risk group. Nevertheless, the patient's needs and resource availability must be considered when determining the frequency of monitoring.
The consensus among the Malaysian expert panels regarding the post-closure treatment and follow-up has been summarised in Table IX.

MEDICAL THERAPY IF PFO IS NOT CLOSED DESPITE AN INDICATION FOR CLOSURE

In certain instances, a patient may decline PFO closure despite being indicated for PFO closure. If this occurs, medical therapy such as antiplatelet or anticoagulant can be considered.[21]

Antiplatelet medications, such as aspirin, and anticoagulants, such as rivaroxaban, dabigatran, and warfarin, are the treatments of choice for patients, although the superiority of one over another has never been conclusively proven. In the RESPECT ESUS trial, although dabigatran did not significantly lower the risk of recurrent stroke in the general population, it did demonstrate a stroke reduction specifically in older stroke patients compared to aspirin.[58] Even though there were no differences in stroke recurrence rates between aspirin and rivaroxaban in the NAVIGATE ESUS trial, the risk of bleeding was significantly higher in the rivaroxaban group.[59] Therefore, the choice of medical therapy should be on a case-by-case basis. Patients with additional risk factors such as a large shunt or ASA, those with multiple infarcts, the presence of deep vein thrombosis, and the elderly may benefit from anticoagulant therapy.[29] Otherwise, antiplatelet therapy was reasonable to consider as the first choice for ESUS patients who were not considered for PFO closure if there was no other justification for anticoagulation.[9,29,44,54,60]

The consensus among Malaysian expert panels regarding the medical therapy if PFO is not closed despite an indication for closure has been summarised in Table X.

CREATING AWARENESS ABOUT PFO CLOSURE IN ESUS

Creating awareness among Malaysian clinicians regarding the management of PFO in ESUS patients is crucial. This will help clinicians in performing adequate PFO and ESUS screenings and initiating early therapy.

Malaysian experts supported the industry's role in sponsoring training and education initiatives at general neurology meetings and events. Introducing PFO management in ESUS via online training and national forums could raise awareness. Providing technicians with screening training should enhance their ability to diagnose PFO.

Continuous medical education (CME) at the hospital might be useful to keep the clinician up to date on the latest PFO management in ESUS.

Long-term follow-up of stroke patients with a PFO among the Malaysian population may help to establish better management approaches for secondary stroke prevention in our local setting. Further research and developing a standardised national registry on PFO management in Malaysia may aid in this endeavour.

The Malaysian expert panels suggested raising awareness regarding PFO closure in ESUS by implementing the strategies outlined in Table XI.

CONCLUSION

The role of PFO in ESUS is not well understood due to many uncertainties in this condition, and it is often under-recognised in Malaysia. It is essential to identify PFO and

other aetiologies of ESUS in stroke patients and promptly refer them to appropriate clinicians with expertise and facilities. The list of public hospitals and institutions currently offering PFO closure services in Malaysia can be found in Appendix B. Multidisciplinary involvement and action are needed to determine the diagnosis and prognosis of the patient. A shared decision-making process would help determine the patient's optimal management. Even though the most effective management for this condition has not yet been established, continuous efforts should be made to improve clinicians' awareness of this condition and begin the necessary screening and treatment. Data on PFO studies continues to evolve and, as such, the consensus recommendation currently put forward by Malaysian experts may evolve too in the future. Therefore, this consensus should provide an overview of how ESUS patients with PFO should be managed locally in Malaysia until robust evidence from more clinical trials emerges in the future.

ACKNOWLEDGEMENTS

We thanked the Director-General of the Ministry of Health (MOH) Malaysia for allowing us to publish this article. We would also like to acknowledge all the Malaysian PFO-Stroke Working Group experts listed in Appendix A for their contributions to the consensus meetings and discussions.

FUNDING

The consensus meetings were organised and supported financially by Abbott Medical (Singapore) Pte Ltd.

CONFLICT OF INTEREST

The authors declared no conflict of interest. There was no influence from the industry in the decision-making process during the preparation of the consensus.

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Appendix A

Malaysian PFO-Stroke Working Group Experts

Neurologists

Dr. Ahmad Shahir Mawardi
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Ang Chong Lip
KPJ Ipoh Specialist Centre
Ipoh, Perak

Dr. Asha Prerna
Loh Guan Lye Specialist Centre
George Town, Pulau Pinang

Dr. Chai Chiun Hian
KPJ Kuching Specialist Hospital
Kuching, Sarawak

Dr. Chia Yuen Kang
Hospital Queen Elizabeth
Kota Kinabalu, Sabah

Dr. Hiew Fu Liong
Sunway Medical Centre
Petaling Jaya, Selangor

Assoc. Prof. Dr. Hoo Fan Kee
Hospital Pengajar Universiti Putra Malaysia,
Universiti Putra Malaysia (UPM)
Serdang, Selangor

Dr. Hor Jyh Yung
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Irene Looi
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Khairul Azmi Ibrahim
Hospital Sultanah Nur Zahirah
Kuala Terengganu, Terengganu

Dr. Law Wan Chung
Hospital Umum Sarawak
Kuching, Sarawak

Dr. Linda Then Yee Yen
Hospital Umum Sarawak
Kuching, Sarawak

Dr. Loo Lay Khoon
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Mohd Azman M Aris
Hospital Melaka
Bandar Melaka, Melaka

Dr. Ong Beng Hooi
Kedah Medical Centre
Alor Setar, Kedah

Dr. Rishikesan Kuppusamy
Pantai Hospital Kuala Lumpur
Bangsar, Kuala Lumpur

Dr. Rose Izura Abdul Hamid
Hospital Raja Perempuan Zainab II
Kota Bharu, Kelantan

Dr. Sally Tee Sow Kuan
Pantai Hospital Kuala Lumpur
Bangsar, Kuala Lumpur

Dr. Sapiah Sapuan
Hospital Sungai Buloh
Sungai Buloh, Selangor

Dr. Sathindren T. Santhirathelagan
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Shanthi Viswanathan Shanthakumar
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Sim Bee Fung
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Sim Siew Hung
Borneo Medical Center
Kuching, Sarawak

Dr. Siva Seeta Ramaiah
Subang Jaya Medical Centre
Subang Jaya, Selangor

Dr. Stefanie Hung Kar Yan
Hospital Tengku Ampuan Rahimah
Klang, Selangor

Dr. Tan Kenny
Loh Guan Lye Specialist Centre
George Town, Pulau Pinang

Dr. Teh Pei Chiek
Hospital Tuanku Ja'afar
Seremban, Negeri Sembilan

Dr. Wan Asyraf Wan Zaidi
Hospital Canselor Tuanku Muhriz,
Universiti Kebangsaan Malaysia (UKM)
Kuala Lumpur

Dr. Wong Sing Keat
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Wong Yee Choon
Pantai Hospital Penang
Bayan Lepas, Pulau Pinang

Dr. Zariah Abdul Aziz
Hospital Sultanah Nur Zahirah
Kuala Terengganu, Terengganu

Cardiologists

Dr. Annamalar Muthu Muthuppalaniappan
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Liew Houng Bang
Hospital Queen Elizabeth II
Kota Kinabalu, Sabah

Dato' Dr. Muhamad Ali S K Abdul Kader
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Saravanan Krishinan
Hospital Sultanah Bahiyah
Alor Setar, Kedah

Dato' Dr. Yap Yee Guan
Sunway Medical Centre
Petaling Jaya, Selangor

Paediatrics Cardiologist

Assoc. Prof. Dr. Abdul Rahim Wong
Universiti Sultan Zainal Abidin
Kuala Terengganu, Terengganu

Dr. Amir Hamzah Abd Rahman
Hospital Tengku Ampuan Afzan
Kuantan, Pahang

Dr. Geetha Kandavello
Institut Jantung Negara
Kuala Lumpur

Dr. Koh Ghee Tiong
Hospital Serdang
Kajang, Selangor

Dr. Leong Ming Chern
Institut Jantung Negara
Kuala Lumpur

Dr. Martin Wong Ngie Liong
Pusat Jantung Sarawak
Kota Samarahan, Sarawak

Dr. Mohammad Tamim Jamil
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Mohd Rizal Mohd Zain
Hospital Universiti Sains Malaysia
Kubang Kerian, Kelantan

Dr. Siva Rao Muniandy
Hospital Queen Elizabeth II
Kota Kinabalu, Sabah

Geriatricians

Dr. Cheah Wee Kooi
Hospital Taiping
Taiping, Perak

Dr. Teh Hoon Lang
Hospital Sultanah Bahiyah
Alor Setar, Kedah

Internal Medicine Physicians

Dr. Abdul Hanif Khan Yusof Khan
Hospital Pengajar Universiti Putra Malaysia
Universiti Putra Malaysia (UPM)
Serdang, Selangor

Dr. Aznita Ibrahim
Hospital Sultan Abdul Halim
Sungai Petani, Kedah

Dr. Lee Aik Kheng
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Neoh Kar Keong
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Zainura Che Isa
Hospital Sultan Abdul Halim
Sungai Petani, Kedah

Medical Officer

Dr. Stephenie Ann Albart
Clinical Research Centre
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Appendix B

List of public hospitals and institutes that are currently offering PFO closure services in Malaysia. (Last updated: 22.07.2022)

List of public hospitals/institutes offering PFO closure services	Location
Hospital Pulau Pinang	Georgetown, Penang
Hospital Queen Elizabeth II	Kota Kinabalu, Sabah
Hospital Raja Perempuan Zainab	Kota Bharu, Kelantan
Hospital Serdang	Serdang, Selangor
Hospital Universiti Sains Malaysia	Kota Bharu, Kelantan
Institut Jantung Negara	Kuala Lumpur
Pusat Jantung Sarawak	Kota Samarahan, Sarawak
Pusat Perubatan Universiti Malaya	Kuala Lumpur

Risk of colorectal cancer due to *Streptococcus gallolyticus*: a systematic review

Edre Mohammad Aidid, DrPH[1], Mohd Shaiful Ehsan Shalihin, MMED FAM MED[2], Azmi Md Nor, MMED Surgery[3], Hairul Aini Hamzah, PhD[4], Nurul Fatihah Ab Hamid, MBBS[5], Nur Arfa Nadhirah Saipol Bahri, MBBS[5], Nuha Dini Abd Ghani, MBBS[5]

[1]Department of Community Medicine, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, [2]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, [3]Department of Surgery, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, [4]Department of Basic Medical Science, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, [5]Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: World Health Organization (2019) has declared colorectal cancer (CRC) as the second most common cancer in females and third in males, where the incidence seems to rise year by year. One of the very few potential pathogens specifically associated with malignant colonic diseases is Streptococcus gallolyticus (Sg). Sg is a part of the intestinal flora which formerly known as biotype I of Streptococcus bovis, belongs to Group D streptococci. Owing to only a few researches done in determining evidence to support Sg as a determinant of CRC, a systematic review is constructed.

Materials and Methods: Full-text articles on case-control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using Google Scholar, PubMed and JSTOR. People of all age groups and Sg bacteraemia or colonisation were the type of participant and exposure used for the search strategy, respectively. Data collection was done by three reviewers and checked by two reviewers for discrepancies. All the papers were critically appraised using the STROBE statement. Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison.

Result: Seven out of 11 articles that fulfil the eligibility criteria were selected. Four papers have low overall risk of bias due to low confounding or selection bias. Sg is found to be a risk factor for CRC from three papers studied, whereas the other four papers did not include the strength of association. Only two papers studied the association between the distribution of Sg and stages of CRC, where the results were contradictory from each other, making it to be inconclusive. The most common method used for Sg detection is a culturing technique, followed by molecular and biochemical techniques.

Conclusion: There is insufficient evidence to prove the association between Sg bacteraemia as the risk factor for CRC as well as the association between the Sg distribution and stages of CRC. Culturing technique is the most common method used for the detection of bacteria, but it requires subsequent investigations to confirm the presence of Sg. Thus, it is recommended that more studies need to be done using strong statistical analysis to control for most of the confounders with comprehensive explanation and use of more methods in the detection of Sg.

KEYWORDS:
Streptococcus gallolyticus, colorectal cancer, case–control studies, cohort studies, systematic review

INTRODUCTION

World Health Organization 2019 reported CRC as the second most common cancer in females and third in males.[1] In 2018, 861,000 deaths and 1.8 million new cases were notified.[2] The number of new cases is expected to be more than 2.2 million cases which account for 60% increase and 1.1 million deaths by 2030.[3] Among the well-established risk factors are unhealthy nutrition, smoking, ageing, polyps, gene and gastrointestinal infection.[4] One of the very few potential pathogens specifically associated with malignant colonic diseases is Sg.[5]

Sg which is formerly known as biotype I of *Streptococcus bovis*, belongs to Group D streptococci, a broad group of genetically diverse bacteria known as *S. bovis/S.* equinus complex (SBSEC). In 2.5 to 15 percent of people, Sg is a part of the intestinal flora. Various studies have shown that cytokine-based effects of long-lasting bacterial inflammation were the main element of transformative changes in the colorectal mucosa.[2] From several epidemiological studies, it was found that the association of Sg and CRC ranges from 47% to 85%. These variations were almost certainly due to different methods being used for Sg detection or possibly due to differences in selected populations.[6]

Currently, there are a lot of tools used for the detection of Sg but the most common method is still not well established. The same goes with the association of Sg and CRC, where there was only few research made. Hence, a systematic review is done.

MATERIALS AND METHODS

The primary objective of this systematic review is to identify evidence to support Sg bacteraemia or colonisation as a risk

This article was accepted: 11 April 2023
Corresponding Author: Mohd Shaiful Ehsan Bin Shalihin
Email: shaifulehsan@iium.edu.my

factor for colorectal cancer (CRC). Secondary objectives would be to determine the most common method used to detect Sg bacteraemia or colonisation and to know there is any association between Sg load and CRC stages.

Criteria for considering studies for this review:
a. Types of studies: Case–control or cohort study designs.
b. Types of participants: People of all age groups.
c. Types of exposures: *Streptococcus gallolyticus* or Streptococcus bovis.

Search methods for identification of studies (including PRISMA flowchart)
Case–control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using PubMed, J-Store and Google Scholar. A total of 37 full-text articles were selected. Three elements of the search strategy were developed using the Boolean term 'AND' or 'OR':
1. Exposure subject heading: (Streptococcus gallolyticus OR Streptococcus bovis) AND
2. Disease subject heading: ((Colorectal Cancer OR Neoplasm OR Malignancy)) AND
3. Study design subject heading: ((Case-control OR Cohort))

The term searched:
(Streptococcus gallolyticus OR Streptococcus bovis) AND ((Colorectal Cancer OR Neoplasm OR Malignancy)) AND ((Case-control OR Cohort))

The search strategy resulted in a total of seven studies that were included in this review. The PRISMA flow diagram for the search strategy is summarised in Figure 1.

Data Collection and Analysis
Data collection was done by three reviewers and checked by two reviewers, consisting of medical doctor from the Department of Community Medicine and medical students, Kuliyyah of Medicine, International Islamic University Malaysia. All the papers were critically appraised using the STROBE statement.

Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison. Meta-analysis was not done due to difficulty in obtaining some of the estimates which were not reported in the articles.

RESULT

Descriptive Result
Table I depicts the descriptive study of the seven articles selected for the review.

Risk of Bias in Included Studies
The overall risk of bias is based on the author's judgement and discussion with other reviewers for this systematic review as listed in Table II below.

Distribution of Streptococcus gallolyticus according to stages of CRC
Table III shows the distribution of Sg according to stages of CRC in two selected articles.

Most common method of Sg detection in Sg bacteraemia and colonisation
Table IV portrays the comparison of methods and tools used to detect Sg infection in bacteraemia and colonisation.

DISCUSSION

Descriptive Studies
In the current review, we found seven studies that determining the association between Sg with colorectal cancer. The main findings and level of evidence are demonstrated in Tables I and II, respectively. Out of these seven studies, Tsai et al., 2016 and Kwong et al., 2018 has taken other alternative way to Sg infection as a risk factor in colorectal cancer patients by conducting retrospective cohort studies.[7,8]

There was a wide range in number of participants involved in each study. Boltin et al., 2015, Al Sharara et al., 2013 and Kwong et al., 2018 use good cases to control ratio which is more than 4, hence selection bias can be controlled.[8-10] Moreover, the study population in previous studies involved multiple countries, covering each continent which means the association of Sg and colorectal cancer is an established risk factor for the world population and not constricted to certain population only.

Al Sharara et al., 2013 significantly demonstrated those with Sg bacteraemia will have 21.6 times high risk to develop colorectal carcinoma compared to those who not being infected.[10] This is supported by Corredoira-Sánchez et al., 2012 and Kwong et al., 2018 which depict 5.1 and 3.87 times more risk, respectively.[8,11] Boltin et al., 2015 and Tabl et al., 2019 also found a correlation between Sg bacteraemia with colorectal cancer; however, the strength of association is not being divulged by the author.[2,9]

In addition, Rezasoltani et al., 2018 in their paper, they found out there is an association between Sg with colorectal polyp that is showing medium to high dysplasia grade.[12] This finding can be another clue to support the association, taken into account that 90% of cases with benign condition of colorectal polyp is the precursor for developing colorectal cancer.[13] Tsai et al., 2016 on the other hand, revealed those who were diagnosed with colorectal cancer with Sg bacteraemia has 12.37 times the risk of getting comorbid malignancy.[7]

Risk of Bias
There were four studies with low risk of bias. Theoretically, the observation of a case–control study is retrospective. However, all of the case–control studies observed both CRC and Sg simultaneously. One study may have the lowest selection bias as the eligibility criteria were clearly mentioned compared to other studies in which the exclusion criteria for both cases and controls include antibiotic or probiotic utilisation, symptoms of fever and diarrhoea, history of lower

Table I: Descriptive studies

Author	Study Design	Sample Size	Population	Period (Year)	Exposure	Outcome	Odd ratio/relative risk (confidence interval) [p- value]
Boltin et al., 2015	Case–control	15 cases, 103 controls	Patients presenting for colonoscopy Clalit Health Services, Israel	Between January 1998 and December 31, 2014	Streptococcus bovis	Colorectal neoplasia	-
Corredoira-Sánchez et al., 2012	Case–control	98 cases, 196 controls	From a single center (more information is not provided)	Between 1988 and May 30, 2011	Streptococcus gallolyticus subsp. gallolyticus	Colorectal neoplasia	5.1 (3.0–8.6) [<0.05]
Al Sharara et al., 2013	Case–control	10 cases, 200 controls	From database of Microbiological Laboratory at American University of Beirut Medical Center	Between January 1996 and October 2010	Streptococcus bovis	Colorectal neoplasia	21.6 (5.4–86.1) [<0.05]
Tabl et al., 2019	Case–control	35 cases, 20 controls	Patient attending the Departments of General Surgery and Hepatology, University Hospitals	Between October 2016 and August 2018	Streptococcus gallolyticus	Colorectal cancer	-
Rezasoltani et al., 2018	Case–control	87 cases, 31 controls	Patients attending Department of Surgery Taleghani Hospital, Tehran- Iran	Between January 1, 2015 and December 31, 2017	S. bovis/ gallolyticus	Colorectal polyp with medium to high dysplasia grade	-
Tsai et al., 2016	Retrospective cohort	34 cases, 15 controls	From database records of Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan	Between January 2004 and January 2014	Streptococcus bovis with colorectal cancer	Other malignancy	12.376 (2.207–69.402) [<0.05]
Kwong et al., 2018	Retrospective Cohort	662 cases, 3310 controls	Public hospitals in Hong Kong	Between January 1, 2006 and December 31, 2015	Streptococcus bovis	Colorectal cancer	3.87 (2.34–6.42) [<0.05]

Table II: Risk of bias in reviewed studies

Author	Selection bias	Exposure assessment bias	Confounder	Other bias	Overall risk of bias
Boltin et al., 2015	Low	Low	High as strategies to control the confounding factors were not stated	None is identified	Low
Corredoira-Sánchez et al., 2012	High due to lack of description on source population and eligibility criteria for cases and controls.	Low	Low	None is identified	Low
Al Sharara et al., 2013	High because controls were not representative of source population of cases and lack of description on eligibility criteria.	Unsure because method of detection was not elaborated	Low	None is identified	High
Tabl et al., 2019	High because controls were not representative of source population of cases and controls did not fulfill all the eligibility criteria for the cases	Low	Low	None is identified	Low
Rezasoltani et al., 2018	Low	High as only one method was used	High as strategies to deal confounding factors were not stated	None is identified	High
Tsai et al., 2016	Low	Low	Low	None is identified	Low
Kwong et al., 2018	Low	Unsure because method of detection was not elaborated	Low	The possibility of sub-clinical bacteremia causing biases in the statistical estimates	High

Table III: Distribution of Streptococcus gallolyticus according to stages of CRC

Author	Method of Streptococcus gallolyticus detection	Distribution of Streptococcus gallolyticus according to stages		P-value / CI
		Cases	Stages	
Tabl et al., 2019	1. Bacteriological isolation 2. Molecular detection	Sg negative n = 22	Stage 1: 40.9% Stage 2: 18.2% Stage 3: 27.3% Stage 4: 13.6%	>0.05
		Sg positive n = 13	Stage 1: 7.7% Stage 2: 30.8% Stage 3: 46.2% Stage 4: 15.4%	
Kwong et al., 2018	1.Culture	Sg negative with CRC n = 39	Not Mentioned	
		Sg positive with CRC n = 25	Stage 1 or 2: 68% Stage 3 or 4: 32%	<0.05

Table IV: Methods used for detection of Streptococcus gallolyticus in Streptococcus gallolyticus bacteraemia and colonisation

Author	Source of samples	Molecular technique	Culture	Microscopy	Biochemistry
Boltin et al., 2015	Stool, colonic fluid, or colonic tissue				
Corredoira-Sánchez et al., 2012	Blood				
Al Sharara et al., 2013	Blood				
Tabl et al., 2019	Colorectal	tissue, Fecal material			
Rezasoltani et al., 2018	Fecal material				
Tsai et al., 2016	Blood				
Kwong et al., 2018	Blood				
Total		4	6	2	3

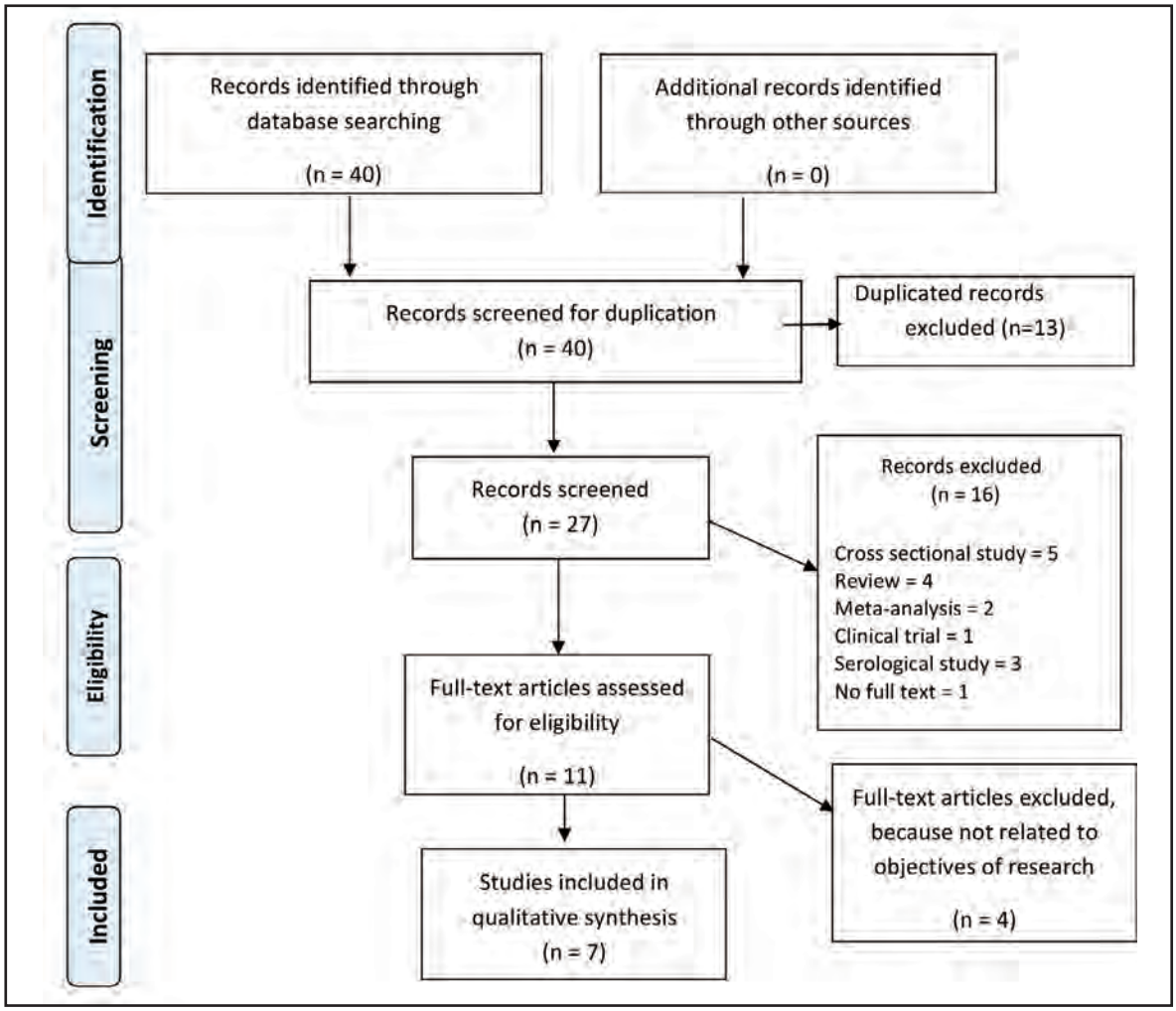

Fig. 1: PRISMA 2009 Flow Diagram.

GI surgery and pregnancy or lactation.[9] These factors were relevant to prevent an altered microenvironment of the large intestine that may lead to bias in Sg measurement.

According to Eshaghi et al.[14], both culture and molecular methods were recommended to obtain a faster result or when there is a possibility of sample infection and late-growing microorganisms. Thus, it is agreed that Sg assessment needs at least two methods of measurement or investigations to avoid bias. For the purpose of discussion, techniques to grow the organism, such as culture, will not be considered as a method of measurement. Four out of seven studies have low exposure assessment bias as they have two methods of Sg measurement and similarly assessed for both case and controls.[2,7,9,11]

Confounder is defined as a variable that has an association with the outcome, associated with the exposure and not a factor in the causal pathway of the disease.[15] Adjustment of confounder is essential to prevent false measurement of association between exposure of interest and outcome. For the purpose of discussion, confounders are considered as well-

known risk factors for colorectal cancer. Most of the studies control the confounders by matching the age and gender of controls to the cases.[2,8,10,11] This is fitting to the study as it is found that male gender has 1.5 times higher risk to develop CRC while old age is a well-known risk factor for CRC.[16]

Distribution of Sg According to Stages

Sg is well-known for its relation to colorectal cancer, and this connection should be thoroughly studied in order to reduce the burden of CRC.[11] In this current review, the percentage of CRC cases according to its stages is looked upon and compared with the distribution of Sg. Recent research by Kwong et al., 2018 showed 68% of CRC patients with positive Sg infection have Stage 1 or 2 CRC compared to only 32% for stages 3 or 4 with the significant association.[8] This is in line with another paper by Abdulamir et al., 2009 which also stated that early-stage adenomas have more incidence with the presence of Sg than later-stage carcinomas.[13] The association between the presence of Sg and these early stages of CRC is vital and might aid in detecting disease sooner, thus preventing further deterioration of diseases. In addition, most patients with colorectal cancer in Malaysia have been diagnosed at a late stage, and if compared with other developed Asian countries, Malaysia has a lower 5-year relative survival by stage.[17] Hence, by knowing these predominant stages of CRC in relation to the distribution of Sg, precautionary measures can be taken appropriately to ensure early detection of disease which can be done with various available methods and tools for Sg identification.

Most Common Method of Sg Detection in Sg bacteraemia and Colonisation

There is wide variation in the association of Sg and CRC across different studies. The discrepancies and variations in association of Sg and CRC across different studies may result from different genetic background, geographical differences as well as different methods for Sg detection or specimens used.[18] To our knowledge, currently, there are no validated tools to diagnose Sg infection. This could be a reason why there are differences in choices of methods and preparation to detect Sg. From the current review, it is found that six out of seven studies use culturing techniques in detecting Sg. However, it is important to note that most of the culture methods were used to grow the bacteria for use in subsequent investigations such as biochemical tests and microscopy. It is found that positive Sg detection almost certainly needs enrichment media.[13] From the bacterial culture, most of the isolates were tested biochemically to identify Sg. A recent study that compares culture and molecular methods in the detection of Sg concluded that both of the methods are currently deemed inadequate or standard, thus both investigations done simultaneously are recommended for the identification of Sg.[14] From this review, it is advocated for future researchers to provide a comprehensive description of Sg detection for further references and more studies done on the tool sensitivity and specificity in the detection of Sg.

CONCLUSION AND RECOMMENDATION

The authors conclude that there was insufficient evidence to prove the association between Sg bacteraemia or colonisation as the risk factor for CRC. Only three out of seven papers that are being studied showed a significant association between these two variables. Plus, the other three papers did not include the strength of association in their study. Hence, they are inconclusive. On the other hand, the association between Sg load and colorectal cancer stages is significantly proved by one study. However, the finding is uncertain considering the high risk of bias. Culturing technique is the most common method used to detect *Streptococcus gallolyticus* bacteraemia or colonisation. Even so, it still requires further investigations to confirm the presence of *Streptococcus gallolyticus*. However, results from this review should be interpreted with caution due to the small number of studies obtained from this systematic review and the possibility of publication bias.

Patients that are found to be infected with Sg in any pathology are recommended to do colonoscopy or faecal occult blood test for CRC screening. More studies need to be done to determine the association between the distribution of Sg and stages of CRC. A comprehensive explanation of Sg detection and two or more methods of detection is recommended for further studies. Further research is warranted using strong statistical analysis to control for most of the confounders as well as to do research for different target populations and meta-analysis of high-quality randomised controlled trials.

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COVID-19 vaccination: a systematic review of vaccination strategies based on economic evaluation studies

Khalsom Samsudin, MPH, Aidalina Mahmud, PhD

Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, Malaysia

ABSTRACT

Introduction: Countries must employ the most efficient way to vaccinate their population with the COVID-19 vaccines, given the vaccines' low availability compared to its demand. This review aims to identify and compare the different COVID-19 vaccine delivery strategies employed internationally in the recent year based on the economic evaluation findings and subsequently to recommend the most cost-effective strategy among them.

Material and Methods: A systematic review was conducted by examining online databases (Scopus, MEDLINE and Science Direct) to identify health economic evaluation studies of COVID-19 vaccines. Critical appraisal of studies was conducted using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).

Results: A total of nine studies were selected for analysis. Results show two strategies that were cost-effective compared to its comparators: mass vaccination program compared to no vaccination and universal vaccination approach compared to a risk-stratified vaccination approach. Several other strategies were found to increase the cost-consequences in the COVID-19 vaccination program: higher vaccine effectiveness, higher vaccination pace, increased vaccination coverage, and vaccine prioritisation for an at-risk population. The study findings were restricted to analysis based on the current available data.

Conclusion: COVID-19 vaccination policies should aim for increased vaccine production as well as a rapid and extensive vaccine delivery system to ensure the maximal value of vaccination strategies. These results can aid policymakers in opting for the most efficient approach to vaccinating the population during this COVID-19 pandemic and future pandemic.

KEYWORDS:
Economic evaluation; cost-effectiveness; COVID-19; vaccine

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic had significantly affected the global community, infecting over 635 million people with over 6.6 million deaths as of 6 January 2023.[1] To curb the spread of infections during early stages of the pandemic, countries adopted non-pharmacological approaches such as lockdowns and social distancing policies. Unfortunately, these resulted in severe economic repercussions. In essence, lockdowns and social distancing policies resulted in reduced demand and supply of goods[2], increased unemployment as well as crisis in foreign investment[3], manufacturing, media and tourism industries.[4] It was estimated that the global unemployment in 2020 was 114 million jobs[5] with the loss of global working hours at around 8.8%, which was approximately four times greater than during the global financial crisis in 2009.[5] The global merchandise trade volume was expected to fall by 9.2% in the year 2020.[6] Additionally, the world tourism lose up to USD 1.2 trillion from the pandemic.[7] The projected loss of revenue for the global sports industry in 2020 was estimated around 57% from 2019 revenue, equivalent to USD 73.7 billion.[8] Consequently, the global gross domestic product (GDP) in the year 2020 was estimated to contract by 5.2%.[9] Worse still, the economic impact of COVID-19 was not uniform across countries and population groups.[2] The estimated GDP contraction from the pandemic varied between countries as follows: for low-income countries GDP contracted as by 5.2%, middle-income countries (8.7%) and high-income countries (6.4%).[9] Across population groups, women 10, people with low education[5], low-skilled workers[5] and the low-income population were severely impacted by COVID-19.[11,12] Small-and medium-sized businesses were severely affected.[13]

The COVID-19 pandemic and the non-pharmacological approaches to controlling its spread also have serious impact on health and wellbeing. The World Health Organization (WHO) estimated that the total excess deaths from COVID-19 were 3 million people.[14] The COVID-19 pandemic was expected to contribute towards undernourishment of up to 132 million people around the world in 2020.[15] Globally, around 100 million people were expected to fall into extreme poverty.[16] The prevalence of depression during COVID-19 was expected to be 25%, higher than the global estimate at 3.44%.[17] School closures had forced 1.2 billion students to be out of school.[18] Hence, the best way out of this calamity is to vaccinate the world population.

COVID-19 Vaccines

COVID-19 vaccines are imperative to prevent serious illness[19], reduce hospitalisation, thus saving lives and costs.[20] COVID-19 vaccination is expected to ease social restriction measures[21], therefore people can resume near-normal daily activities and revive the economy.[22] Hence, vaccination is critical for global economic recovery.[23] Revival of the

This article was accepted: 17 April 2023
Corresponding Author: Aidalina Mahmud
Email: aidalina@upm.edu.my

economy is an important aim for the world population as better economy is associated with higher life span, healthier children, fewer disabilities and mortalities.[24] Thus, COVID-19 vaccination is expected to be of high value to society. For instance, it was estimated that installed capacity for 3 billion annual vaccine courses for COVID-19 is associated with a global benefit of USD 17.4 trillion, equivalent to USD 5800 per course.[25]

By the end of 2020, there were already COVID-19 vaccines manufactured to be distributed to the world population. However, the global demand for vaccine exceeded the supply.[26] For some countries, despite vaccine availability in global market, governments were facing issues with vaccine costs27 and securing finances for vaccine purchase.[26] As a result, these issues warranted countries to find the most efficient way to achieve allocation efficiency. In general, immunisation strategies selection depends on the goal of vaccination; for example, routine vaccination given to a specific population cohort aimed for elimination or containment of certain disease[28], mass vaccination strategies targeted a large number of population, aimed for rapid containment of a disease during an emerging or ongoing epidemic, or specific immunisation campaign targeted for any disease not included in routine immunisation or for specific additional population groups.[28]

Within the context of existing knowledge, several factors influence the overall outcome of COVID-19 vaccination. The fundamental factor is the vaccine efficacy. The recommended efficacy of a COVID-19 vaccine was set at a minimum of 50% in order to be licenced for use[29], 70% efficacy for epidemic prevention, and 80% to end an epidemic without any other public health measures.[20] In addition, the benefits of any COVID-19 vaccine will also depend on vaccination coverage[20,30], and the pace of vaccination.[20] Within the constraints in vaccine supply, obtaining an optimal reduction in mortality and morbidity can be achieved by prioritising vaccination for people at higher risk for severe COVID-19 disease, in particular, the elderly.[30,31] The environmental condition also affects the outcome of COVID-19 vaccination, in particular, introducing the vaccine at the time of low COVID-19 community transmission rate will produce more desirable outcome in disease and mortality reduction.[32]

Vaccination strategies permit countries to provide effective vaccination policies to produce the optimal output in terms of reduction of disease and deaths from COVID-19.[25] The selection of vaccination strategies to achieve allocative efficiency requires careful planning and evidence-based decision-making.[28] Hence, evidence from economic assessment is fundamental to make these informed decisions.[28]

Health Economic Evaluation

An economic evaluation is a systematic approach to compare the cost and consequences of two or more alternative interventions to foster accountability and transparency in decision-making.[33] Several types of economic evaluation studies include cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).[33] In economic evaluation, the main focus is on which alternative intervention provides the best value for the resources spent? Conducting economic evaluation studies in the COVID-19 vaccination program allows policymakers to determine the value of different vaccination strategies for appropriate program planning.

In economic evaluation, a perspective is the point of view adopted when deciding the types of costs and health benefits to be included.[34] For instance, the payer perspective usually includes the cost of medical treatment and relevant social and clinical services[34] while the societal perspective encompasses all direct and indirect costs borne by the provider, payer, and patients.[34]

The cost-consequences of an economic evaluation are described in several ways. The results of a CEA are commonly expressed as incremental cost-effectiveness ratio (ICER) using the formula.

ICER= (Cost for intervention A - Cost for intervention B) / (Effectiveness for Intervention A - Effectiveness for intervention B)

In essence, the ICER describes the additional costs that an intervention imposes over another compared to the additional benefits it delivers.[35] If a new intervention (intervention A) is less costly and more effective than the comparator (intervention B), intervention A is described as cost-saving or dominant.[35] However, if intervention A is more costly yet more effective than B, then the ICER value can objectively determine how much more costly intervention A is from B compared to the extra benefits that intervention A can give.[36] Ultimately, the decision to select the new intervention will depend on how much value the provider, patient, or society is willing to pay for additional effectiveness obtained from a new intervention.[37] A similar concept is also applied to the incremental cost-utility ratio (ICUR), except that the measure of consequences in ICUR is the utilities – either quality-adjusted life years (QALY) or disability-adjusted life years (DALY).[35]

A CBA describes both cost and consequences of an intervention in the form of monetary value.37 The results can be described as a benefit-cost ratio (BCR) which is calculated from this formula

Benefit-cost ratio (BCR) = (Total benefit) / (Total costs)

The BCR described the value of benefits obtained for every unit of monetary value spent for the intervention costs.[33] A BCR of more than one generally indicates that the total benefit value of an intervention is more than its costs.[33]

Another measure of cost-consequences is the net monetary benefit (NMB), calculated using the following formula

Net Monetary Benefit (NMB) = $\Delta E \lambda - \Delta C$

where E refers to effectiveness measure, λ refers to willingness-to-pay and C refers to cost.[33] The NMB result of greater than zero indicates that the respective intervention is cost-effective.[37]

As countries develop their COVID-19 immunisation programs to alleviate the pandemic, there is a need to

identify the strategies that provide maximum value by means of the overall cost-consequences. Hence, this review's aims are two-fold: to identify the different strategies of COVID-19 vaccination and compare them based on the economic evaluation findings and to recommend the most cost-effective strategies of COVID-19 vaccination available to date. This review addresses the question, "What are the strategies that facilitate the achievement of the optimal value from COVID-19 vaccination programs?"

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used to conduct and report this systematic review.[38] Published articles were collected from three databases: Scopus, Ebscohost/Medline and Science Direct with data search dated up to 23 June 2021. A key term search strategy was employed using the combination of the following keywords:

(cost-effectiveness OR cost-utility OR cost-benefit OR 'economic evaluation') AND (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (vaccine OR vaccination OR immunisation)

Articles were selected using the following inclusion criteria: (i) conduct any economic evaluation study in the form of cost-effectiveness, cost-utility, or CBA, and (ii) available in the English language. We excluded CMA studies as CMA studies emphasise only on costs while assuming similar outcome for interventions under comparison. A reviewer (K.S) conducted the screening and selection process. All the articles in selected databases were screened, duplicates were removed and titles and abstracts were scanned for relevancy of the research questions and objectives. Articles not meeting the inclusion criteria were removed, and reasons for exclusion were noted. In the event of uncertainty, the reviewer (K.S) discussed with another reviewer (A.M) to reach a consensus related to the article selection. Study qualities were appraised using The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[39]

The systematic review was based on the PICO themes – Population, Intervention (vaccination strategy), comparator and outcome (consequences)[40] when data were extracted from the studies.

Key information was collected from the selected articles using a data extraction table. The studies were then categorised into groups of strategies with similar characteristics (themes), namely i) comparing vaccination vs no vaccination, ii) vaccine efficacy/effectiveness, iii) comparison of different population strategies, iv) strategy based on anaphylaxis reaction, v) vaccine coverage and vi) pace of vaccination. In each of these themes, the studies were evaluated based on their outcome measures to determine if they are efficient or otherwise. The cost-consequences measure selected for this review can be presented as any of the following: cost-effectiveness (measured in cost-effectiveness ratio (CER), incremental cost-effectiveness ratio (ICER) or net monetary benefit (NMB), or benefit-cost ratio (BCR) and were measured at any time horizon of interest depending on the specific study. These measures were obtained from texts, tables or appendices within the selected articles.

RESULTS

A total of nine studies met the selection criteria and requirements for our review. Figure 1 shows the search strategy process. Six studies were conducted in high-income countries.[41-46] while three were conducted within the context of middle and low-income countries.[47-49] For the cost-consequences analysis, four studies adopted provider perspective[41,42,44,48], two studies used societal perspective[43,45] and two studies applied both.[46,47] Additionally, one study specifically adopted donor perspective to demonstrate the cost-consequences of vaccination strategies in low- and middle-income countries.[49]

All studies utilised various modelling methods for the estimation of cost-consequences, in particular decision tree model[45], Markov model[42,43,46], microsimulation model[48,49], continuous-time model[41] or transmission model.[44,47] All studies analysed estimated direct costs, referring to the costs of vaccine purchase and delivery system as well as the costs from managing COVID-19 infections (including hospitalisations and critical care). On the other hand, some studies also include indirect costs, referring to productivity loss from loss of work days from attending vaccination and experiencing vaccine side effects[46] or COVID-19 infections[43,46,47] and productivity loss from premature deaths.[47] The time horizon of selected studies ranges from 180 days or 6 months[41,46], 1 year[42,43,45,47-49] and 10 years.[44]

The studies included in this review have modelled different strategies to gain the optimal value from COVID-19 vaccination programs. These strategies include having a vaccination program versus no vaccination[41,42,43], comparing different vaccine efficacy[44,46,47,48], strategies linked to prioritisation of population at-risk for COVID-19[41,42], having a universal program versus risk-stratified program (based on anaphylaxis reaction) [45], as well as comparing different pace[48] and coverage[48,49] of a vaccination programme.

These studies have demonstrated several key findings: (i) having a vaccination policy is cost-saving or cost-effective as compared to having no vaccination programme, (ii) vaccination strategy by utilising a higher vaccine efficacy is more cost-effective, (iii) prioritising vaccination for at-risk population is cost-effective, (iv) a mass vaccination strategy is cost-effective even with the risk of anaphylaxis reaction, (v) the pace of vaccination roll-out affects cost-effectiveness and (vi) providing higher vaccination coverage is more cost-effective. The summary of studies characteristics and results are included in Table I.

Vaccine is Cost-Saving or Cost-Effective as Compared to No-Vaccination Strategy

Several studies have documented that adopting a vaccination policy was cost-saving as compared to the absence of any vaccination strategy. In the USA, a vaccination programme was estimated to be able to reduce health costs by 90% and reduce disease burden by 50%.[43] Additionally, from societal perspective, the COVID-19 vaccination program in the USA was estimated to reduce

Table I: Descriptive studies

Country	Author (Year)	Perspective	Model	Time Horizon	Cost	Cost-Consequences Measure	Results
Denmark	Debrabant et al., (2021)[41]	Provider	Continuous Time Model Based on SEIR	6 months	Direct	ICER per life years	**Comparing different vaccination strategies vs no vaccination** • Vaccination of 1.5 million persons ≥ 60 years old was cost-effective (ICER = USD 11,150/LYS) • Vaccination of 1.5 million persons < 60 years old was cost-effective (ICER = USD 11, 359/ LYS) • Vaccination of 900,000 persons < 60 years old & 1.5 million person ≥ 60 years old was cost-effective (ICER = USD 25, 208/ LYS)
USA	Padula et al., (2020)[43]	Societal	Markov Model With SEIR	1 year	Direct Indirect	ICER per QALY	• Vaccination programme dominates the no-intervention approach (ICER = USD - 8,854/QALY)
USA	Kohli et al, (2020)[42]	Provider	Markov Model	1 year	Direct	ICER per QALY	**Different vaccine strategies vs no vaccine** • Vaccination using age-based prioritization scheme dominates no vaccination • Vaccination using risk-based prioritization scheme dominates no vaccination • Vaccination based on occupational-based prioritization was cost-effective (ICER =USD 20,000 / QALY saved)
USA, UK & Canada	Shaker et al., (2021)[45]	Societal	Decision-tree model	1 year	Direct	ICER per death prevented	• Universal vaccination (vaccinating everyone irrespective of history of anaphylaxis) dominates risk-stratification vaccine strategy (people with a history of anaphylaxis reaction excluded from vaccination) (ICER = -USD 66,201/death prevented) • Compared to no vaccination, a vaccination programme yield an incremental NMB ranging from £12·0 billion - £334·7 billion
UK	Sandman etal., (2021)[44]	Provider	Dynamic transmission model	10 years	Direct	NMB	**Vaccination effectiveness scenario vs no vaccination** • In the worst-case scenario (having vaccine efficacy of 50% and 45-week immunity duration), the NMB range between –£1·1 billion and £56·9 billion • In the best-case scenario (having vaccine efficacy 95% with 3 years immunity duration), the NMB range from £12·0 billion to £334·7 billion across different physical distancing scenarios
Turkey	Hagens et al., (2021)[47]	Provider & Societal	Dynamic Transmission Compartmental Model	1 year	Direct Indirect	ICER per QALY	**Comparison of vaccine effectiveness (VE) vs No vaccine** • From provider perspective, having a more effective vaccine (VE on transmission (90%) & VE on disease (90%)) was cost-effective (ICER = USD 511/ QALY) • From provider perspective, having a less effective vaccine (VE on transmission (45%) & VE on disease (90%)) was still cost-effective (ICER = USD 1045/ QALY) • From societal perspective, utilization of both vaccines with different effectiveness were cost-saving as compared to no vaccination

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Table I: Descriptive studies

<table>
<tr><th>Country</th><th>Author (Year)</th><th>Perspective</th><th>Model</th><th>Time Horizon</th><th>Cost</th><th>Cost-Consequences Measure</th><th>Results</th></tr>
<tr><td>LMIC</td><td>Siedner et al., (2021)[49]</td><td>Donor</td><td>Discrete Microsimulation Model</td><td>1 year</td><td>Direct</td><td>ICER per infection prevented and life years saved</td><td>Comparing different vaccine coverage
• Achievement of 20% vaccine coverage was cost-effective compared to no vaccination
• Compared to 20% vaccine coverage, increment of vaccine coverage to 50% was cost-effective with increasing ICER
<table><tr><th>Vaccine coverage</th><th>ICER/Infection prevented</th><th>ICER/YLS</th></tr><tr><td>20%</td><td>USD 20</td><td>USD 250</td></tr><tr><td>30%</td><td>USD 40</td><td>USD 870</td></tr><tr><td>40%</td><td>USD 80</td><td>USD 2,820</td></tr><tr><td>50%</td><td>USD 150</td><td>USD7,240</td></tr><tr><td>70%</td><td>USD 760</td><td>USD 41,900</td></tr></table>• Vaccination coverage of 67% of the population was cost-saving as compared to no vaccination</td></tr>
<tr><td>South Africa</td><td>Reddy et al., (2021)[48]</td><td>Provider</td><td>Dynamic state-transition Monte-Carlo Microsimulation Model</td><td>1 year</td><td>Direct</td><td>ICER per life years saved</td><td>Comparison of different vaccination coverage vs 40% coverage
• Vaccine coverage 67% was cost-effective compared to 40% vaccination coverage (ICER = $9,960/YLS)
• Vaccination coverage 80% showed an estimated ICER of $4,270/YLS compared to 40% vaccination coverage</td></tr>
<tr><td>Israel</td><td>Wang et al., (2021)[46]</td><td>Provider and Societal</td><td>Markov model with SIR approach</td><td>180 days</td><td>Direct Indirect</td><td>BCR (with effectiveness measure in QALD)</td><td>Comparison of different vaccine pace scenario vs no vaccination
• Vaccination pace of 150,000 vaccination/day dominated the no vaccination strategy
• 200,000 vaccination/day was dominated lower vaccination pace
• 300,000 vaccination/day dominates lower vaccination pace
• Vaccination utilizing any vaccine with a coverage rate of 70% was dominant against no vaccination

Benefit–cost ratio of different vaccines
BCR1: Saving on medical cost divided by the direct cost of vaccine (provider perspective)
BCR2: Saving on the (direct medical cost + indirect cost) divided by direct cost of vaccine (societal perspective).
BCR: Cost saving on (direct medical cost + indirect cost + economic impacts of productivity + education loss) divided by investment on vaccine.
BCR4: Benefit from life saved from vaccination divided by investment on vaccine.
<table><tr><th></th><th colspan="3">Vaccine</th></tr><tr><th></th><th>Moderna</th><th>Pfizer</th><th>Astra Zeneca</th></tr><tr><td>BCR1</td><td>2.79</td><td>4.77</td><td>7.21</td></tr><tr><td>BCR2</td><td>6.05</td><td>10.39</td><td>14.46</td></tr><tr><td>BCR3</td><td>13.54</td><td>23.32</td><td>28.85</td></tr><tr><td>BCR 4</td><td>175.84</td><td>23.32</td><td>28.85</td></tr></table></td></tr>
</table>

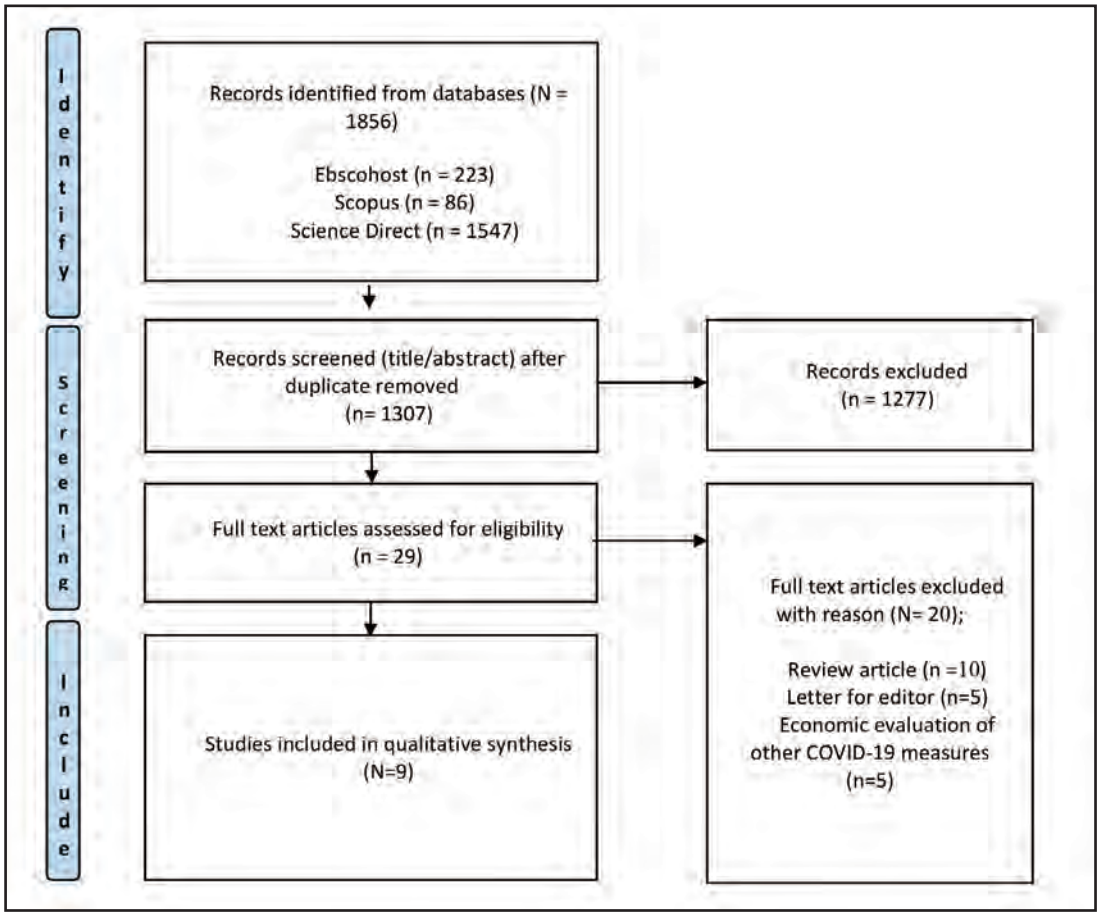

Fig. 1: The PRISMA flowchart for the selection of EBSCOhost

societal costs to only USD 9.9 billion, a 98% cost reduction compared with no intervention.[43] Within the societal perspective, immunisation not only reduces the cost of treating COVID-19 but allows people to be healthy and able to work to provide for society in general. Therefore, as the societal perspective considered the costs related to the loss of productivity from COVID-19 infections, a vaccination strategy provides significant benefits to society.[46] Within the context of South Africa, an immunisation program targeted to cover 67% of the population was also determined as cost-saving as compared to no vaccination.[48] In the United Kingdom, an effective vaccination was expected to minimise community transmission without the need for long-term physical distancing policies, therefore, estimated to yield incremental net monetary values ranging from £12 billion to £334·7 billion for 10 years.[44]

Meanwhile other studies demonstrated that a vaccination policy was cost-effective compared to no vaccination.[47,49] For example, a vaccination program for low- and middle-income countries (LMIC) with donor investment of USD 6.4 billion to achieve 20% coverage would be highly cost-effective resulting in an incremental cost-effectiveness ratio (ICER) of USD 20 for every infection prevented and USD 250 per year of life saved (YLS) compared with no vaccination.[49] Hence, highlighting the need for the global community to support LMIC with the necessary resources to vaccinate large proportions of their populations and ensure equity in vaccine distribution.[49]

Vaccination Strategy by Utilising a Higher Vaccine Efficacy is More Cost-Effective

As COVID-19 vaccines prevent COVID-19 infections and reduce the severity of COVID-19 disease, studies had demonstrated consistent findings, whereby a higher vaccine efficacy resulted in better cost-effectiveness. A Turkish study demonstrated that for vaccines with 45% effectiveness in disease transmission and 90% effectiveness in disease reduction, the incremental cost-effectiveness ratio (ICER) was USD 1045 per QALY saved, which was considered cost-effective.[47] However, if the vaccine had higher effectiveness in disease transmission (90%) with similar effectiveness in disease reduction (90%), the ICER reduced to an even better value of USD 511 per QALY [47], which demonstrates that the selection of a vaccine with higher effectiveness gives more value for a vaccination programme. Similarly, the model from the UK demonstrated that with higher vaccine effectiveness and a long duration of induced immunity, the net monetary benefit of a vaccination program will increase.[44]

From the societal perspective, despite variability in the effectiveness of available vaccines, having a vaccination strategy was cost-saving as compared to no vaccination.[46] A study from Israel concluded that despite variable vaccine effectiveness, the benefit-cost ratio (BCR) of mass vaccination against COVID-19 with three current available vaccines was cost-saving for gaining more lives and less costs incurred.[46] In addition, when the global economy and education losses

were taken into consideration, the benefit-cost ratio for the three vaccines was inflated.[46]

Prioritising Vaccination for At-Risk Population is Cost-Effective

Studies had found that a vaccination strategy by prioritising vaccine provision is cost-effective. For example, in Denmark, the inclusion of the elderly population 60 years of age or older was more cost-effective than a vaccination strategy targeting only those younger than 60 years old.[41] A study from the USA demonstrated that in the event of vaccine supply constraint, prioritising vaccination of persons over age 65 appears to be cost-saving because of the high cost from higher incidence of intensive care and ventilation.[42] For similar reason, a prioritisation scheme to high-risk groups defined by a residency in nursing homes (without consideration of age) was also found to be cost-saving as compared to no vaccination strategy.[42] Finally, prioritising vaccination based on occupation, whereby those considered to have a priority occupation i.e., healthcare personnel and emergency care workers are given vaccination priority was estimated to be cost-effective compared to no vaccination, as demonstrated by the value of ICER of USD 20,000 for every quality-adjusted life year (QALY) saved.[42]

Even with Risk of Anaphylaxis Reaction: A Mass Vaccination Strategy is Cost-Effective

The occurrence of anaphylaxis cases after COVID-19 vaccination had prompted health authorities in some countries to issue a precaution for vaccination in those with a history of a severe drug or vaccine reaction or severe food allergy.[45] As a result, a model was constructed to compare between a universal vaccination policy (no restriction of vaccination) and a risk-stratified approach (person with a history of anaphylaxis contraindicated from vaccination).[45] From a healthcare perspective, a universal vaccination strategy dominates risk-stratification. However, when the risk of vaccine-associated anaphylaxis exceeded 0.8%, the risk-stratified approach was the most cost-effective strategy.[45] The findings of this study suggested that a universal vaccination strategy gives more value to healthcare providers and overall society. However, if the risk of vaccine anaphylaxis is more than 0.8%, a risk-stratified approach should be considered.[45]

The Pace of Vaccination Affects Cost-Effectiveness

Studies have documented that having a faster vaccination pace produces maximal benefits in reducing the number of populations affected by COVID-19. In the case of South Africa, it was demonstrated that an immunisation programme with the highest vaccination pace (300,000 vaccinations daily) dominates the lower vaccination pace (200,000 and 150,000 vaccinations per day).[48] In other words, a higher pace of vaccine roll-out resulted in the most favourable clinical outcomes and lowest total costs incurred to the healthcare provider.

Providing Higher Vaccine Coverage is More Cost-Effective

Studies showed that increasing the vaccination coverage does not only have a significant reduction in morbidity and mortality but was more cost-effective.[48,49] Within the context of South Africa, a 67% population vaccination coverage resulted in ICER of USD 9,960 per life years as compared to 40% of vaccine coverage which was considered cost-effective. However, increasing the vaccination coverage to 80% will reduce the ICER value (USD 4,270 per life years), meaning that higher vaccination coverage is more cost-effective.48 Interestingly, within the context of the LMIC, with vaccination coverage increasing from 20% to 50%, the ICER value persistently increased, albeit the results were still cost-effective.[49] However, beyond 50% vaccination coverage, the ICER continued to increase, suggesting that the reductions in infections and deaths continued, despite its diminishing efficiency.[49] In essence, having better vaccination coverage of provides value much value to the health provider as well as the society.

DISCUSSION

Within the context of this review, economic evaluation studies had consistently provided compelling evidence that nationwide vaccination policies for COVID-19 provide massive value for the healthcare providers and overall society. Given the severity of the pandemic and the number of lives lost due to COVID-19, the resource investment for a vaccination strategy was expected to be lower than the costs for treating COVID-19 diseases. Even with the high cost of vaccination programme, it is still considered as cost-effective to provide COVID-19 vaccination to the population.

The limited supply of COVID-19 vaccines during the early phase of the pandemic had forced countries to select different strategies of vaccine distribution and roll-out. Hence, not only is it valuable to have a vaccination policy in a country during the pandemic, it is also vital to ensure that the vaccination policies are designed to ensure optimal outcomes in terms of prevention of mortality and morbidity as well as improving quality of life of the population. Therefore, different vaccination strategies should be planned for different population context. In the scenario of a limited vaccine supply, a strategy concentrated on prioritised vaccination of the pockets of the population which were at the most risk of hospitalisation and death is crucial and gives the most benefit. Therefore, countries are recommended to prioritise vaccination for people at risk and subsequently extend vaccine roll-out to populations at lower risk. For countries and international bodies, this review also highlights the importance of concentrating efforts to accelerate vaccine roll-out to improve the pace and coverage of COVID-19 vaccination. This is possible by establishing effective vaccine distribution and administration systems to ensure prompt vaccine delivery to the community to gain the most benefit from COVID-19 vaccination. As concerns of vaccine hesitancy hamper the efforts to introduce new vaccines and achieve adequate population coverage [50], the value of COVID-19 vaccination not only rely on the ability to provide sufficient vaccine access [49], but also depends on countries' ability to address vaccine hesitancy in the community. Higher vaccine hesitancy is expected to decrease demand for vaccine[50], subsequently reducing the value of COVID-19 vaccination strategies, which necessitates strategic measures to investigate and address COVID-19 vaccine hesitancy within the context of respective countries.

Within the global community, strategies to improve global vaccine production, addressing the bottlenecks of vaccine production as well as ensuring equity in vaccine distribution

is fundamental to ensure that the global population will benefit from the COVID-19 vaccines. Hence, the collaboration of various stakeholders is necessary to achieve vaccine equity.

LIMITATIONS

There are several limitations to this review. First, the cost-effectiveness or cost-consequences value was bounded by the various parameters and assumptions included in the economic evaluation studies. At this point, as much information is still unknown related to vaccine effectiveness, namely the duration of induced immunity and effectiveness against different COVID-19 variants, interpretation of the findings should be taken within the context of current, available data. Secondly, most studies conducted simulations for a brief time horizon of one year or less and based on the current pandemic situation. Hence, these studies did not provide information related to the value of COVID-19 vaccination in the long run. With the introduction of booster doses and the possibility of COVID-19 vaccination activities become seasonal or regular in the future, cost-effectiveness measures should be investigated depending on the future available data and context. Third, the outcomes selected for these studies (for example, QALY, life years, or death prevented) were mainly based on the direct impact of COVID-19 infections, hence the cost-effectiveness value is expected to be a conservative estimation. Although some studies included societal perspective and took into consideration the productivity loss from COVID-19 and economic gain from vaccination, there is still a multitude of health and social impact of prevention of COVID-19 morbidity and mortality (such as the resumption of health services towards pre-pandemic level, improved physical and mental health as community return to work and school) as well as the return of international travel norm. Therefore, taking these factors into consideration, the value of COVID-19 vaccination is expected to be higher. Fourth, studies often did not consider issues related to COVID-19 vaccination hesitancy that may impair COVID-19 vaccination effectiveness in the population. Finally, as COVID-19 vaccination is a relatively new intervention with potential rapid publications of more economic evaluations, there is a need to revisit this review in future.

CONCLUSION

In summary, the vaccination programme is a valuable tool to combat the COVID-19 pandemic across the world. Various strategies affect the cost consequences of COVID-19 vaccination programme, namely the prioritisation of high-risk population, vaccine effectiveness as well as the pace and coverage of vaccination. Hence, it is recommended that the international and national actors involved in the global vaccination effort to take these factors into consideration for future COVID-19 vaccination policies.

The COVID-19 pandemic has demonstrated a unique case of providing global vaccination to achieve the most benefit within a short duration of time. Within this context, it is recommended that all countries should strive for a rapid and effective vaccine distribution by providing an effective delivery system and addressing vaccine hesitancy among the population. The future directions recommended include having more economic evaluations done at various levels of population-based vaccination programs to help policymakers in efficiently allocating scarce resources especially for COVID-19 and other vaccine-preventable diseases. Economic evaluation for vaccination programs should be done early on such as at the start of a pandemic, and this can be done using disease or mathematical modelling approaches so that the findings of these evaluations can be used in a timely manner when policies are drafted for the implementation of the vaccination programs.

For countries with issues related to COVID-19 vaccine supply and distribution, the focus is on providing early vaccine distribution to at-risk population while strengthening effort to achieve access to vaccine supply and improving the healthcare system to provide efficient vaccine delivery. Additionally, collaborative international efforts should be employed to assist countries with severe COVID-19 vaccine supply problems. This can be done by offering either financial assistance, technology advancements or the technical expertise to ensure that these countries are able to receive adequate vaccine supply as well as designing their effective vaccine delivery and distribution system.

ACKNOWLEDGEMENT

The authors would like to thank everyone who provided their opinions in order to improve this article.

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SARS-CoV-2 associated posterior reversible encephalopathy syndrome (PRES) – a review of 82 cases

Josef Finsterer, PhD

Neurology and Neurophysiology Center, Vienna, Austria

ABSTRACT

Objectives: Severe, acute, respiratory syndrome-coronavirus-2 (SARS-CoV-2) infections can be complicated by central nervous system (CNS) disease. One of the CNS disorders associated with Coronavirus Disease-19 (COVID-19) is posterior reversible encephalopathy syndrome (PRES). This narrative review summarises and discusses previous and recent findings on SARS-CoV-2 associated PRES.

Methods: A literature search was carried out in PubMed and Google Scholar using suitable search terms and reference lists of articles found were searched for further articles.

Results: By the end of February 2023, 82 patients with SARS-CoV-2 associated PRES were recorded. The latency between the onset of COVID-19 and the onset of PRES ranged from 1 day to 70 days. The most common presentations of PRES were mental deterioration (n=47), seizures (n=46) and visual disturbances (n=18). Elevated blood pressure was reported on admission or during hospitalisation in 48 patients. The most common comorbidities were arterial hypertension, diabetes, hyperlipidemia and atherosclerosis. PRES was best diagnosed by multimodal cerebral magnetic resonance imaging (MRI). Complete recovery was reported in 35 patients and partial recovery in 21 patients, while seven patients died.

Conclusions: PRES can be a CNS complication associated with COVID-19. COVID-19 patients with mental dysfunction, seizures or visual disturbances should immediately undergo CNS imaging through multimodal MRI, electroencephalography (EEG) and cerebrospinal fluid (CSF) studies in order not to miss PRES.

KEYWORDS:
Infection, SARS-CoV-2, COVID-19, coronavirus, posterior reversible encephalopathy syndrome

INTRODUCTION

There is increasing evidence that Coronavirus Disease-19 (COVID-19) manifests not only in the lungs but also in several other organs.[1] In addition to the lungs, the extra-pulmonary organ most frequently affected is the central nervous system (CNS).[2] CNS manifestations of COVID-19 are very diverse.[2] One of these CNS disorders associated with COVID-19 is posterior reversible encephalopathy syndrome (PRES).[2] PRES is a rare disorder clinically characterised by headache, visual disturbances, mental changes and seizures.[3] PRES is thought to be a syndrome of impaired autoregulation or endothelial dysfunction leading to preferential posterior circulation hyperperfusion.[4] The symptoms of PRES usually come on quickly and can be serious and life threatening. When treated with antihypertensive drugs or anti-seizure drugs, the symptoms often disappear within days or weeks. PRES occurs in patients with high blood pressure, eclampsia, severe infections, kidney disease and certain autoimmune disorders. It can also occur in patients treated with certain anticancer drugs and immuno-suppressants. PRES is diagnosed on the basis of the clinical presentation and the magnetic resonance imaging (MRI) findings.[4] On MRI, PRES associated lesions are usually located in the occipital areas and present as hyperintensity on diffusion weighted imaging (DWI) and hyperintensity on apparent diffusion coefficient (ADC) maps (vasogenic edema). Vascular irregularities are frequently observed. PRES is also characterised by spontaneous resolution of these lesions within a few days or weeks.[5] PRES can also be accompanied by bleeding (haemorrhagic PRES). Differential diagnoses of PRES include acute demyelinating encephalopathy (ADEM), which reposnds to steroids, immune-encephalitis, viral encephalitis, ischemic stroke, mitochondrial stroke-like lesions, cerebral vasculitis, drug-induced leukoencephalopathy, Wernicke encephalopathy and pontine and extra-pontine myelinolysis. PRES is increasingly recognised as a complication of COVID-19.[3] This narrative review summarises and discusses previous and recent findings on severe, acute, respiratory syndrome- coronavirus-2 (SARS-CoV-2) associated PRES.

METHODOLOGY

A literature search was conducted in the databases PubMed and Google Scholar using the search terms "SARS-CoV-2", "COVID-19" and "coronavirus" combined with "PRES", "posterior reversible encephalopathy syndrome", "arterial hypertension", and "visual impairment". In addition, reference lists of available articles were searched for further suitable references. It included the articles that provided detailed information on patients infected with SARS-CoV-2 who experienced PRES. Articles that were not accessible or only available as an abstract or articles in language other than German, English, French or Spanish were excluded.

This article was accepted: 18 May 2023
Corresponding Author: Josef Finsterer
Email: fifigs1@yahoo.de

Table I Patients with SARS-CoV-2 associated PRES published as per the end of February 2023

Age	G	LOCOP (d)	Presentation	RR	Comorbidities	SeverityC	Outcome	Reference
90	f	21	seizure, CI	227/95	DM, AHT, DVT, PE, AFLU	severe	CR after4 months	[13]
36-70	4f, 4m	1-70	seizure, CI	nr	DM, AHT, HLP, RI, ASKL LTX, DVT, OSA, OB	severe	CR (3), dead (1)	[11]
46	m	nr	seizure, CI	160/90	SM, AHT, OB	severe, MV	CR	[14]
70	m	10	confusion	124/72	Asthma, AHT, ASKL	severe, MV	death	[8]
10	m	nr	seizure	109/70	none	severe,	CR	[15]
48	m	18	MD	180/90	OB	severe, MV	PR	[16]
67	f	nr	MD	178/83	AHT, DM, HU ASKL, asthma	severe, MV	PR	[16]
74	m	15	seizure	150/nr	myeloma	moderate	PR	[17]
67	f	25	MD	193/97	AHT, OB, DM	severe, MV	PR	[18]
58	m	24	MD	189/122	HLP, AHT	severe, MV	CR	[18]
64	f	35	MD, vision ↓	nr	AHT, HU, HLP, AFIB, OSA	severe, MV	CR	[19]
63	f	37	seizure	nr	AHT	severe, MV	CR	[20]
27	f	nr	MD	nr	none	severe	death	[10]
74	f	nr	confusion, agitation, MW	237/nr	HLP, DM, HOT	severe, MV	PR	[21]
64	m	nr	confusion, NCSE	184/nr	nr	severe, MV	PR	[21]
73	m	nr	confusion, seizure	212/nr	nr	severe, MV	CR	[21]
65	f	nr	MD	190/nr	AHT, DM	severe, MV	PR	[21]
69	f	nr	seizure, delirium, mutism	200/116	ASKL	mild	PR	[22]
24	f	nr	delirium, confusion, MW	nr	none	severe, MV	PR	[23]
35	f	0	seizure, blindness	nr	HOT	asymptomatic	nr	[24]
33	f	nr	hallucinations, palinopsy	nr	none	mild	CR	[25]
46	m	13	MD, agitation, MW	130/70	AHT, DM	severe, MV	PR	[26]
66	f	10	MD, seizure	160/nr	nr	severe; MV	death	[9]
59	m	12	confusion	173/96	nonw	severe, MV	death	[12]
64	m	30	seizure, NCSS, MW	nr	nr	severe, MV	CR	[27]
55	m	nr	seizure, anopia, MW	nr	nr	severe, MV	PR	[27]
63	f	nr	seizure, impaired vision	nr	nr	severe, MV	CR	[27]
68	m	nr	MW, impaired vision	nr	nr	severe, MV	PR	[27]
64	f	35	MD, impaired vision	nr	nr	severe, MV	CR	[27]
57	f	9	seizure, MW, aphasia	nr	nr	severe, MV	PR	[27]
61	f	nr	MD, seizure	187/98	none	severe, MV	PR	[28]
52	f	34	seizures	180/97	HIV, RI	severe, MV	PR	[28]
25	f	1	seizure, headache	190/120	none	mild	PR	[29]
54	f	31	seizure, aphasia, anopia	125/78	none	severe, MV	PR	[30]
55	m	7	confusion, lethargy	171/85	AHT, OB, RI, SM, OSA, HLP	mild	CR	[31]
85	m	nr	MD	184/96	AHT, DM, AFIB, RI	asymptomatic	CR	[32]
43	f	1	seizure, lethargy	nr	sickle cell disease, epilepsy	nr	CR	[33]
69	f	17	seizure, halluzinations	180/90	AHT, HLP	severe, MV	PR	[34]
55	f	13	MW, anopia, seizure	178/88	AHT, DM	severe, MV	nr	[34]
65	m	39	seizure	140/100	AHT, DM, pyoderma	severe, MV	CR	[34]
9	m	8	seizures, vomiting	143/92	none	mild	CR	[35]
66	m	16	seizure, IC	nr	AHT, HLP	severe, MV	CR	[36]
64	m	14	IC	170/100	AHT, HLP	severe, MV	CR	[36]
54	f	nr	aphasia, acalculia, FAS, CB	nr	none	mild	PR	[37]
9	m	21	seizure, hallucinations, MD	79/55	none	severe, MV	PR	[38]
30	m	nr	seizure, MD, hemorrhage	nr	none	severe, MV	death of COVID	[39]
nr	f	nr	seizure, headache, lethargy	nr	lupus on cyclophosphamide	asymptomatic	CR	[40]

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Table I Patients with SARS-CoV-2 associated PRES published as per the end of February 2023

Age	G	LOCOP (d)	Presentation	RR	Comorbidities	SeverityC	Outcome	Reference
38	m	14	seizure, aphasia, CB, CI, IC	130/80	steatosis, alcoholism	severe	CR	[41]
62	f	41	seizure	nr	AHT, OB	severe, MV	CR	[42]
5	f	5	seizure, CB	RR ↑	none	severe	CR	[43]
33	f	8	headache, MD, CB	nr	gestational DM, migraine, HOTsevere	CR	[44]	
61	f	24	seizure	nr	nr	severe, MV	CR	[45]
64	f	nr	drowsiness, impaired vision	nr	nr	nr	nr	[46]
74	f	5	confusion, CB, disorientation	170/100	AHT, HLP, AFIB	severe	nr	[47]
nr	nr (n=4)	nr	nr	nr	nr	nr	nr	[48]
90s	f	3	seizure, confusion, hemiplegia	131/63	AHT	severe	nr	[49]
nr	nr	nr	altered mental state	nr	nr	severe, MV	nr	[50]
nr	nr	nr	altered mental state	nr	nr	severe, MV	nr	[50]
54	m	nr	nr	nr	nr	nr	nr	[7]
38	m	10	confusion, agitation, CB	130/80	none	severe	CR	[51]
38	f	3	seizure, confusion, anopia	nr	none	moderate	PR	[52]
nr	nr	nr	nr	nr	AHT	nr	CR	[53]
48	m	nr	disorientation	nr	nr	moderate	nr	[54]
7	f	nr	seizure, CB	nr	none	mild	nr	[55]
8	m	37	MD, nystagmus, seizure	nr	metastatic medulloblastoma	mild, MV	death	[56]
52	f	7	impaired vision	146/72	nr	severe, MV	CR	[57]
9	f	10	seizure, IC	RR ↑	none	moderate	CR	[58]
78	f	nr	delirium	nr	AHT, rheumatoid arthritis	severe	nr	[59]
66	f	nr	CB, confusion, disorientation	nr	AHT, DM, 10 asthma	severe, MV	CR	[60]
39	f	11	MD, IC, seizure	nr	LTX on cyclosporine, MM	severe	CR	[61]
34	f	nr	seizure, confusion	210/110	primigravida	asymptomatic	CR	[62]
67	f	nr	seizure, disorientation	150/88	ASKL	severe	CR	[63]

AFLU: Atrial flutter, AHT: Arterial hypertension, ASKL: Atherosclerosis, CB: Cortical blindness, CI: Cognitive impairment, CR: Complete recovery, d: Days, DM: Diabetes mellitus, DVT: Deep vein thrombosis, FAS: Foreign accent syndrome, G: Gender, HLP: Hyperlipidemia, HOT: hypothyroidism, HU: Hyperuricemia, IC: Impaired consciousness, LOCOP: Latency between onset of COVID-19 and onset of PRES (days), LTX: Liver transplantation, MD: Mental deterioration, MM: Mycophenolate mofetil, MV: Mechanical ventilation, MW: Muscle weakness, NCSE: Non-convulsive status epilepticus, NR: Not reported, OB: Obesity, OSA: Obstructive sleep apnoea, PE: Pulmonary embolism, PR: Partial recovery, severity: Severity of COVID-19, RI: Renal insufficiency, RR: Blood pressure at onset of neurological manifestations or on admission, SM: Smoking

RESULTS

A total of 56 articles were identified, reporting a total of 82 patients with SARS-CoV-2 associated PRES (Table I).[8-63] Ages were reported for 74 patients and ranged from 5 to 90 years. Gender was specified for 75 patients and was 34 male and 41 female. The male to female ratio was 1:1.2. Some of the trapped females were pregnant without suffering from eclampsia. PRES has been reported much more frequently in adults than in children and adolescents. Only five of the included patients were paediatric patients (Table I). The latency between the onset of COVID-19 and the onset of PRES was reported in 48 patients and ranged from 1 day to 70 days (Table I). In nine patients the latency was > 30 days. Blood pressure at admission or highest blood pressure during hospitalisation was reported in 48 patients and was elevated > 125/85 mmHg in 28 patients (Table I). A total of 24 patients had a history of arterial hypertension, 12 had a history of diabetes/gestational diabetes and 10 had hyperlipidemia (Table I). Five had atherosclerosis and three hypothyroidism (Table I).

Clinical presentation of PRES was reported in 76 patients. The most common presentations of PRES were mental deterioration (n=47) seizures or non-convulsive status epilepticus (n=46) and visual impairment (n=18). Nine patients were reported to have muscular weakness, six patients were described with impaired consciousness. Aphasia was reported in four patients and three patients developed delirium (Table I). Hallucinations were reported in three patients (Table I). The clinical presentation of SARS-CoV-2 associated PRES did not differ from non-SARS-CoV-2 associated PRES. PRES was best diagnosed by multimodal cerebral MRI. Few patients had cerebral CT without MRI.[49,53,63] MRI most commonly showed bilateral cortical and subcortical T2/FLAIR hyperintensities in the occipital region. The frontal and parietal regions, but also the basal ganglia and the cerebellum were less frequently affected.[41-63] On multimodal MRI these lesions most commonly presented as vasogenic oedema. Cytotoxic oedema and haemorrhage were rarely observed.[40] Six patients presented with haemorrhagic PRES on imaging.[16,39,48,54,56] Electroencephalography (EEG) was rarely reported and was either normal or showed only diffuse slowing without epileptiform discharges.[41] Cerebrospinal fluid (CSF) studies were rarely performed and were either normal or showed slightly elevated protein.[41]

The severity of COVID-19 was reported in 74 patients. The severity of COVID-19 was classified as "severe" in 58 cases, 39 of which required mechanical ventilation. Four patients were asymptomatic, eight had mild COVID infection, and four had moderate COVID-19 (Table I). The outcome was reported in 63 patients. Full recovery was achieved in 35 patients and partial recovery in 21 patients, while seven patients died (Table I). Regarding the cause of death in seven of the included patients, two patients died from sepsis with multi-organ failure[8,9], one from cardiopulmonary arrest,[10] two patients from respiratory failure,[12,39] one from severe intracerebral bleeding[56] and one with status epilepticus.[11] According to these data, only one patient died as a result of PRES.[11] In none of these cases was an autopsy reported.

DISCUSSION

This review shows that SARS-CoV-2 infections can be complicated by PRES. Morphology, clinical presentation, course and outcome of SARS-CoV-2 associated PRES do not differ from PRES due to other causes. There is a slight excess in females. Although all the age groups can be affected, predominantly adults are affected. Mental deterioration, seizures and visual disturbances are the most common presentations of SARS-CoV-2 associated PRES. SARS-CoV-2 associated PRES particularly occurs in patients with severe COVID-19 and most patients recover either fully or incompletely. No specific risk factors that predispose to the development of PRES could be identified. However, possible contributing factors that could favour the development of SARS-CoV-2 related PRES include arterial hypertension, diabetes and hyperlipidaemia.

The reason why PRES develops in COVID-19 patients is unclear, but it can be speculated that it may be due to severe arterial hypertension, endothelial damage resulting from immune system activation, impaired vascular autoregulation or blood–brain barrier dysfunction.[3] The inflammatory storm has been suggested to pathophysiologically injure the endothelium, resulting in endothelial dysfunction, interstitial fluid extravasation and cerebral oedema, however, PRES is not usually associated with an increase in brain volume.[7] Since COVID-19 is accompanied by a strong immunologic response, immune endotheliopathy is the most likely explanation.[7] The immune hypothesis is supported by the fact that PRES occurs frequently in patients taking immunomodulatory medication and in patients with increased systemic inflammation, such as in autoimmune disease, sepsis, or organ transplants and that it has been reported in association with other immunologic disorders.[64] Impaired autoregulation can also be triggered by renal failure, preeclampsia, or eclampsia, autoimmune disease or immunosuppression.[4] Given the reported slightly higher rates of haemorrhagic PRES in COVID-19 patients,[6] it can be speculated that COVID-19 patients with PRES develop higher blood pressure, a more severe vasculopathy or damage of the blood–brain barrier, or more commonly coagulopathy than patients with PRES due to other causes.

Regarding the short interval between the onset of COVID-19 and the onset of PRES in some patients, it can be speculated that infection with SARS-CoV-2 occurred much earlier than a day before (incubation time 4-14 days) and that it was either asymptomatic or was only mildly symptomatic and therefore went undetected for several days. It is also conceivable that the virus entered the body and triggered the immune response days before the clinical manifestations of COVID-19 and PRES appeared almost simultaneously.

Limitations of the review are that it had a narrative design and therefore some published cases of SARS-CoV-2 associated PRES may have been missed and that data were not analysed statistically. Another limitation is that the data provided in several publications are often reported incompletely and therefore contribute to the pile of "missing data". An article was not added due to concerns from the Cureus editor. Another case was not included because he also had Miller-Fisher syndrome. In nine cases, the latency between the onset

of COVID-19 and the onset of neurological manifestations was > 30 days, making a causal relationship unlikely.

CONCLUSION

This review demonstrates that posterior reversible encephalopathy syndrome (PRES) can be a central nervous system (CNS) complication of COVID-19 and that patients with COVID-19 plus mental dysfunction, seizures or visual impairment should undergo immediate CNS imaging, electroencephalography (EEG) and cerebrospinal fluid (CSF) studies. Because patients with severe COVID-19 develop PRES particularly during hospitalisation in an intensive care unit (ICU), it can be easily missed when patients are not awake or not undergoing prospective cerebral imaging. Although the prognosis of PRES is good in most cases, neurologists must remain vigilant that SARS-CoV-2 infections can be complicated by PRES and that these patients require immediate evaluation and treatment to improve their outcome.

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Acknowledgement
May Issue 2023

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

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