Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 77

Issue No: 4

July 2022

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

MJM

Official Journal of the Malaysian Medical Association

Volume 77 Number 4 July 2022

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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Subscription Rates:
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Printed by: Digital Perspective Sdn. Bhd.
42-1, Level 1, Plaza Sinar, Taman Sri Sinar, 51200 Kuala Lumpur. Tel: 03-6272 3767
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The Medical Journal of Malaysia
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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

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Books and Other Monographs:
Personal Author(s)
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Chapter in Book
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Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

Other Articles:
Newspaper Article
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All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

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Severe cutaneous adverse reactions: A 5-year retrospective study at Hospital Melaka, Malaysia, from December 2014 to February 2020

Chiaw Ting Tee, MRCP(UK), Noor Hairiza Binti Abdullah, MD(UNIBRAW), Punitha Kristummoonthy, MD(MMA), Choon Sian Lee, AdvMDerm(UKM)

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ABSTRACT

Introduction: Severe cutaneous adverse reactions (SCARs) are potentially lethal adverse drug reactions that involve the skin, mucous membranes, and internal organs, resulting in disability. SCARs include drug-induced epidermal necrolysis, which is Steven Johnson syndrome (SJS)/ Steven Johnson syndrome and toxic epidermal necrolysis overlap (SJS-TEN overlap)/ toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), generalised bullous fixed drug eruption (GBFDE), and acute erythroderma. Awareness of local epidemiology of SCARs plays an important role in prescribing practices by healthcare provider. Recognition of SCARs enables the offending drug to be withdrawn immediately, which is the definitive treatment of SCARs.

Materials and Methods: This is a retrospective study reviewing SCAR cases reported to the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) registry at the Department of Dermatology, Hospital Melaka, for 5 years and 3 months from December 2014 to February 2020.

Results: A total of 41 SCARs cases were identified over the study duration. The incidence rate was 0.18%. All 41 cases require hospitalisations, with four cases (9.8%) managed in ICU and one mortality (2.4%) due to SJS-related complication. One patient had two episodes of SCARs. There were 22 male patients and 18 female patients. The majority were Malays (33, 80.5%), followed by Chinese (7, 17.1%) and Indonesian (1, 2.4%). There was no Indian patient with SCARs in this study. The mean age of patients was 47.2±17 years. Drug-induced epidermal necrolysis was the commonest type of SCARs (63.4%), and out of this, SJS accounted for the majority of cases (48.8%). Antibiotic was the main group of offending medication in this SCAR study (29.3%). The top five individual causative drugs of SCARs in sequence include allopurinol, phenytoin, carbamazepine, co-amoxiclav, and cephalexin. Allopurinol was the commonest culprit drug for drug-induced epidermal necrolysis and DRESS, phenytoin for acute erythroderma, and co-amoxiclav for AGEP.

Conclusion: SJS was the most common manifestation and Allopurinol was the commonest culprit drug for SCAR cases in our cohort.

KEYWORDS:
Severe cutaneous adverse reactions, Allopurinol, Drug-induced epidermal necrolysis

INTRODUCTION

Cutaneous adverse drug reaction (cADR) is defined as undesirable change in the structure or function of the skin, its appendages, or mucous membranes caused by a drug. cADRs are classified into severe and non-severe reactions. Severe cutaneous adverse reactions (SCARs) are a group of potentially lethal adverse drug reactions that involve the skin, mucous membranes, and internal organs, which results in persistent or significant disability, requiring hospital admission, intensive care, or specific interventional treatment. SCARs encompassed (1) drug-induced epidermal necrolysis (Steven Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], SJS-TEN overlap), (2) drug reaction with eosinophilia and systemic Symptoms (DRESS), (3) acute generalised exanthematous pustulosis (AGEP), (4) generalised bullous fixed drug eruption (GBFDE), and (5) drug-induced acute erythroderma.[1,2] Each SCAR has its own characteristic cutaneous presentations, causative drugs, clinical courses, and treatment modalities.

SCARs can occur in patients of any age, ranging from children to elderly. Medications are the leading trigger of SCARs. Antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDS) are the common groups of drugs responsible for SCARs.[1] Hence, the decision to initiate any treatment should be justified to prevent or reduce unnecessary morbidity or mortality. It is very important to acquire knowledge on SCARs because it implies great impact on morbidity, mortality, and hospital costs. Therefore, treating physicians should promptly recognise SCARs through the identification of their characteristic clinical features, so that the offending drug is withdrawn immediately and supportive therapies are administered.

SCARs are diagnosed mainly based on clinical history, physical cutaneous finding, blood investigation, and skin biopsy at lesser extent. Hospital-based studies are expected to detect more cases of SCARs, as they are referral centres for close monitoring and management of SCARs that can cause fatalities. Various hospitals worldwide reported the characteristics of SCARs where the data were obtained mainly from respective dermatology clinics. Awareness of local

This article was accepted: 06 May 2022
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epidemiology of SCARs play an important role in prescribing practices by healthcare provider. Hence, a retrospective review of all patients referred to the Department of Dermatology, Hospital Melaka, Malaysia, from December 2014 to February 2020 ,was carried out to determine the local epidemiological patterns and the common drugs implicated.

MATERIALS AND METHODS

This is a retrospective study comprising 5-year and 3-month data (December 2014 to February 2020) collected from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) registry, and dermatology records from the Department of Dermatology, Hospital Melaka, Malaysia.

Drug-induced epidermal necrolysis is characterised by extensive necrosis and detachment of the epidermis, with two or more mucous membrane involvement. For SJS, the epidermal detachment is <10% of body surface area (BSA), TEN involves detachment of >30%, and SJS/TEN overlap described patients with epidermal detachment of 10-30% BSA.[1] DRESS is diagnosed using the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) diagnostic criteria. The criteria include hospitalised patient with acute rash, suspicion of a drug-related reaction, with three out of these systemic features: fever of 38°C, lymphadenopathy involving at least two sites, involvement of at least one internal organ, and haematological abnormalities, such as eosinophilia.[3] AGEP is characterised by numerous small, non-follicular sterile pustules, arising from erythematous base, with high fever and raised neutrophil count. The diagnosis of AGEP is further confirmed histologically, in which spongiform subcorneal and/or intraepidermal pustules with papillary oedema is looked for.[3] GBFDE is defined as fixed drug eruption lesions with widespread blisters and erosions involving more than 10% BSA in at least three out of six sites (head and neck, anterior trunk, back, upper limbs, lower limbs, and genitalia).[1] Drug-induced acute erythroderma is characterised by generalised skin redness affecting more than 90% of the BSA.[3]

All cases with SCARs were identified from MADRAC registry at the Department of Dermatology, Hospital Melaka, and only those labelled as definite, probable, and possible cADR based on Naranjo Classification by the dermatologist were selected. Data on patient demography, clinical patterns, causative drugs, treatment, and clinical outcomes were collected from patients' case notes. Patients' files with incomplete data entry were excluded from analysis.

Data were processed using Microsoft excel XL, SPSS statistics software version 23.0. Numerical variables were described using mean ± standard deviation (SD). Nominal variables were described using frequencies and percentages. Statistical significance was taken at the $p<0.05$ level. Ministry of Health Malaysia Research Ethics Committee (MREC)'s approval was obtained prior to the commencement of study.

RESULTS

A total of 41 SCAR cases were identified over the study duration of 5 years and 3 months. Forty-one cases involved 40 patients, in which one of the patients developed SCARs twice during the study period. There was a male preponderance with 23 cases involving male patients and 18 cases involving female patients. Male preponderance was seen in AGEP as well as acute erythroderma, with the male to female ratio of 4:1 and 7:1, respectively. In contrast, there were more female patients who developed SJS/TEN/SJS-TEN overlap than male patients, with the female to male ratio of 15: 11. However, the gender ratio was equal (1:1) in DRESS.

The majority of patients were Malay, 33 cases (80.5%), followed by Chinese, 7 cases (17.1%), and 1 Indonesian (2.4%). There was no Indian patient with SCARs detected over this study duration in Hospital Melaka. The racial distribution of patients in our department comprised of 64.5% Malay, 26.4% Chinese, 7.5% Indian, and 1.5% from others. SCARs can occur in any age, ranging from children to elderly. The age of SCAR patients in this study ranged from 17 to 77 years, with the mean age of 47.2 years (Table I).

Most of the patients who developed SCARs have underlying comorbidities, with 38 out of 41 cases (92.7%). There were five patients with underlying retroviral disease (12.2%), three with renal impairment (7.3%), and one with underlying malignancy (2.4%). Comorbidity is the main factor leading to polypharmacy. Thirty-six out of 41 cases involved co-administration of medication for the underlying medical condition. This study revealed that almost a quarter of SCAR cases (10 out of 41 cases, 24.4%) occur in patients with prior history of allergy, either to medication or to food. All 41 cases (100%) require hospitalisation, in which four out of 41 cases (9.8%) were managed in intensive care unit. Unfortunately, there was one mortality case due to SJS-related complication.

SJS/TEN/SJS-TEN overlap accounted for the majority of SCAR cases in this retrospective study, as there were 26 cases (63.4%). This was followed by acute erythroderma, eight cases (19.5%), as the second highest SCARs in this study. There were five AGEP cases (12.2%) and two cases of DRESS (4.9%). None of the SCARs was attributed to GBFDE (Figure 1).

Antibiotics were the main causative agents in this SCAR study, as there were 12 cases in total (29.3%). This was followed by 10 cases caused by allopurinol (24.4%) and nine cases attributed to anticonvulsant (22.0%). NSAIDs and antiretroviral (ARV) accounted for one (2.4%) and two cases (4.9%), respectively (Figure 2).

In addition to allopurinol (10 cases, 24.4%), the other top five individual causative drugs in this SCAR study include phenytoin, carbamazepine, co-amoxiclav, and cephalexin (Figure 3). Both phenytoin and carbamazepine resulted in four cases each, which contributed to 9.8% of total cases each, while three cases were related to co-amoxiclav (7.3%) and two cases by cephalexin (4.9%). Allopurinol was the commonest causative drug for SJS/TEN/SJS-TEN overlap and DRESS in this study (six cases of SJS; two cases of TEN; two cases of DRESS), whereas co-amoxiclav was the commonest causative agent for AGEP while phenytoin being the top causative medication in acute erythroderma.

Table I: Demographic and clinical data

Characteristics	n = 41
Male: Female ratio	1.28: 1
Mean age in years (range)	47.2 (17-77)
Ethnicity –	
Malay	33 (80.5%)
Chinese	7 (17.1%)
Indian	0 (0.0%)
Others	1 (2.4%)
Patients with comorbidity	38 (92.7%)
Patients with underlying malignancy	1 (2.4%)
Patients with underlying HIV	5 (12.2%)
Patients with renal impairment	3 (7.3%)
Patients with history of allergy	10 (24.4%)
Patients with polypharmacy	36 (87.8%)
Patients hospitalised	41 (100.0%)
Mortality at acute event	1 (2.4%)
Number of ICU/HDW admission	4 (9.8%)

Table II: A comparison of clinicoepidemiological studies on SCARs in various hospitals, Malaysia

	Melaka (Dec 2014–Feb 2020)	Klang (2009–2013)[4]	Kuantan (2013–2016)[5]	Penang (2006–2015)[1]
Duration of study	5 years 3 months	5 years	4 years	10 years
Total SCAR cases	41	33	25	189
Male: Female ratio	1.28 : 1	1.38 : 1	1 : 1.27	1 : 1.20
Ethnicity	Malay 80.5% Chinese 17.1% Indian 0.0% Others 2.4%	Malay 67% Chinese 24% Indian 6% Others 3%	Malay 64% Chinese 24% Indian 8% Others 4%	Malay 49% Chinese 38% Indian 11%
Mean age	47.2 years	42.8 years	53.7 years	45 years
Age range	17–77 years	7–81 years	4–92 years	2–87 years
The most common SCAR	SJS (48.8%)	SJS (75.8%)	SJS (60%)	SJS (55%)
The most common group of offending medication	Antibiotics (29.3%)	Allopurinol (33.3%)	Antibiotics (44.0%)	Antibiotics (33.3%)
The most common individual causative drug	Allopurinol	Allopurinol	Allopurinol	Allopurinol
Mortality rate	2.4%	9.1%	8.0%	5.8%

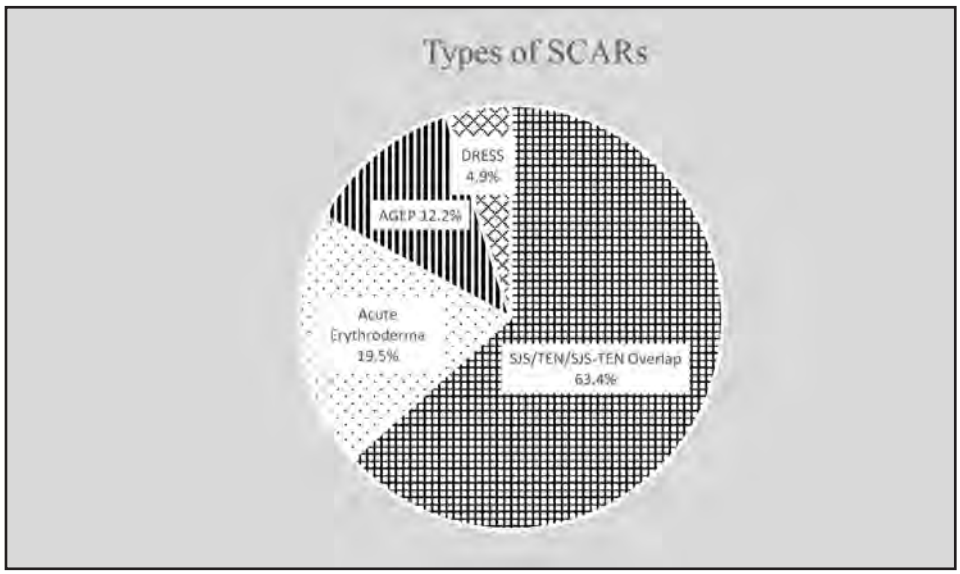

Fig. 1: Types of SCARs

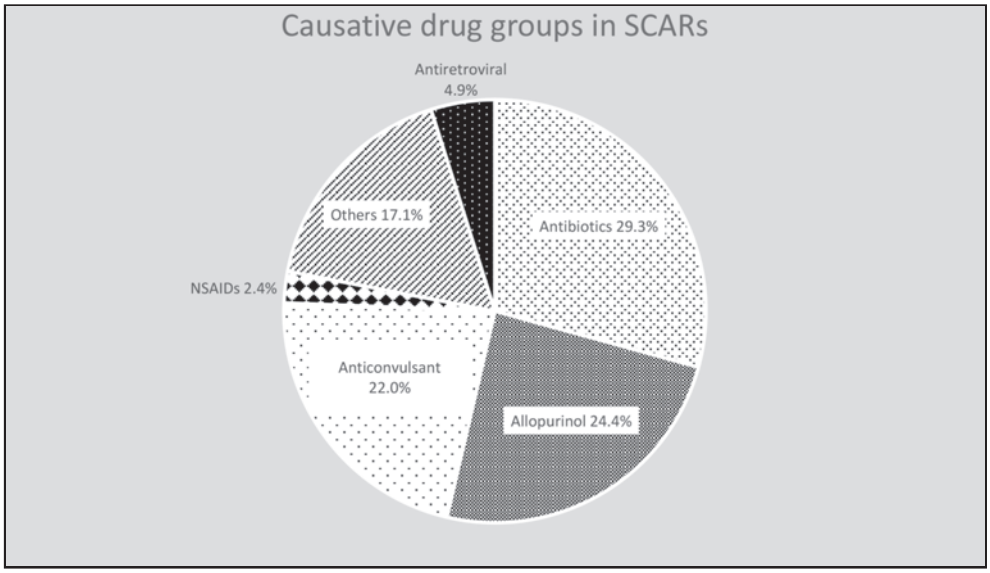

Fig. 2: Causative drug groups in SCARs

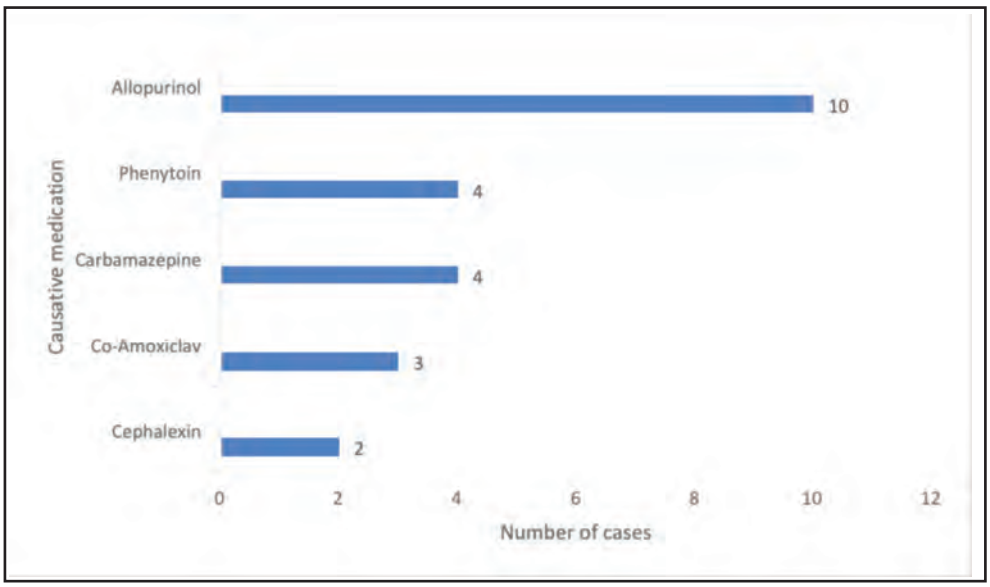

Fig. 3: Top five individual causative drugs

Co-amoxiclav resulting in two cases of AGEP and one case of SJS-TEN overlaps. All four SCAR cases due to phenytoin were acute erythroderma, while all four cases due to carbamazepine were SJS. Two SCAR cases secondary to cephalexin were SJS as well. There was an increasing trend of prescribing allopurinol from year 2014 to 2017, followed by a decline during the subsequent years. Four patients were prescribed with allopurinol for gouty arthritis, and three were prescribed for asymptomatic hyperuricemia, while for the remaining three patients, indication was not stated.

DISCUSSION

Patterns of SCARs and their causative drugs vary among the different populations. Understanding of local epidemiology of SCARs play an important role in prescribing practices. Out of the 260 cases of cADRs referred to the Department of Dermatology, Hospital Melaka, from December 2014 to February 2020, 41(15.8%) were SCARs. There were 22,474 new cases seen during that period, yielding an incidence rate of 0.18%.

The mean age of patients in this study was 47.2 years, with patients' age ranging from 17 to 77 years. There was no

paediatric patient with SCARs reported in this study, although paediatric population was not excluded in the study. This is in contrast with studies done in Klang, Kuantan, and Penang Hospital, with the youngest age groups of 7, 4, and 2, respectively. SCARs in children are not common but potentially serious.[1,4-6] SCARs are more commonly seen with increasing age, as this can be attributed to the associated comorbidities requiring polypharmacy. Almost 92.7% of our cases have comorbidities with 43.9% of patients taking at least one or two concomitant medications. This study showed slight male preponderance with the male to female ratio of 1.28:1. This is similar to the Klang study with male to female ratio of 1.38:1.[4] However, both studies in Kuantan and Penang showed female preponderance, in which the male to female ratios were 1:1.27 and 1:1.2, respectively.[1,5]

One of our patients was diagnosed to have SCARs twice within the study duration. Both the incidence took place in 2017, with the time frame of five months apart. This was a patient with retroviral disease, who developed TEN due to nevirapine, followed by SJS secondary to dapsone five months later. This highlights that cADRs and SCARs are common among patients with retroviral disease.[7] Genetic factors can predispose an individual to SCARs according to pharmacogenomic study. Genetic markers enable elucidation of the pathogenesis of SCARs, as well as screening of susceptible subjects.[8] The HLA alleles associated with hypersensitivity reactions to nevirapine also differ by ethnicity. In Thailand, hypersensitivity to nevirapine is associated with HLA-B*35:05.[9] HLA-B*13:01 is associated with SCARs secondary to dapsone in Asians.[8] A pharmacogenomic study needs to be considered in high-risk patients, especially those with recurrent incidence of SCARs.

Despite the Ministry of Health's effort of changing prescribing category for allopurinol from B (can be prescribed by medical officers) to A/KK (can only be prescribed by consultants/specialists/family medicine specialists) in 2011, allopurinol remains the commonest causative drug for SCARs in the study conducted in Kuantan, Malaysia, from 2013 to 2016.[5] The similar result was obtained in our study cohort, with allopurinol being the commonest drug in total SCARs cases (24.4%), as well as in SJS/TEN/SJS-TEN overlap and DRESS. Continuous reminder of judicious prescribing allopurinol with justified indication is emphasised from time to time, in order to reduce the incidence of SCARs induced by allopurinol. HLA-B*58:01 allele is an important genetic marker in allopurinol-induced SCARs. This is supported by a local study, which revealed strong association between HLA-B*58:01 and allopurinol induced SCARs in multi-ethnic Malaysian population, particularly in Chinese and Malays.[10] Pre-emptive genetic screening should be considered when commencement of allopurinol is absolutely indicated.

In Malaysia, SJS was reported as the most common manifestation of SCARs according to studies done in tertiary hospital in Penang and Kuantan.[1,5] This is consistent with our study, in which SJS was the most common manifestation of SCARs. Drug-induced epidermal necrolysis, which include SJS/TEN/SJS-TEN overlap, accounts for 63.4% of SCARs, and of this, SJS 48.8%, TEN 9.8%, and SJS-TEN overlap 4.9%. Antibiotics were the predominant group of drugs, which contributed to 29.3% of SCARs in our study. This is comparable to 30.3% in Klang Hospital, 33.3% in Penang, and 44.0% in Kuantan studies. This reminds us of more judicious antibiotic usage in the future.[1,4-5]

Contrastingly, a study from Brazil revealed DRESS as the most frequent SCAR presentation and the drugs most frequently involved were anticonvulsants.[11] This discrepancy can be either due to different prescribing practices or genetic predisposition. Although allopurinol was reported as the commonest causative agent for SJS and TEN in Malaysia studies, a study from Nigeria revealed antiretroviral as the commonest offending drug of SJS and TEN, with nevirapine being the most widely implicated drugs.[12]

There was one mortality case (2.4%) in our study, due to SJS-related complication. Mortality rate for studies done in Klang Hospital was 9.1%, in Kuantan Hospital 8.0%, and in Penang 5.8%.[1,4-5] Early drug withdrawal is mandatory in all SCARs. Physicians' knowledge is essential to the improvement of diagnosis and management, as well as prevention of long-term sequelae.

LIMITATION OF THE STUDY

This study is limited by its retrospective design.

CONCLUSION

SJS was the most common manifestation, and allopurinol was the commonest culprit drug for SCAR cases in our cohort. Medicines are to be prescribed when absolutely indicated.

ACKNOWLEDGEMENT

The authors would like to thank the director of Hospital Melaka, Malaysia, for giving us permission to conduct this study at Hospital Melaka.

CONFLICT OF INTEREST

There is no conflict of interest related to this study.

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Biomarker significance of interleukins, IL-37 and IL-38 in patients with juvenile idiopathic arthritis

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ABSTRACT

Introduction: Juvenile idiopathic arthritis (JIA) is the most common rheumatic condition that develops during child age and adolescence. Unbalanced production of pro-inflammatory cytokines is suggested to participate in the etio-pathogenesis of JIA, so the objective of this study is to evaluate the role of interleukins (IL), IL-37 and IL-38, in patients with JIA.

Materials and Methods: Sixty patients with JIA (19 males, 41 females) and 90 healthy controls (35 males, 55 females) were included in this study. Participants were assessed using the juvenile arthritis disease activity score-27 and underwent laboratory tests, including measurements for C-reactive protein, rheumatoid factor, and IL-37 and IL-38.

Results: Mean ages of JIA patients and controls were 10.37±4.21 years and 11.13±3.84 years, respectively. Compared to controls, serum IL-37 levels were increased in patients with JIA (117.98±209.282ng/ml vs. 37.87±24.496ng/ml; p<0.01), whereas serum IL-38 titres were diminished in individuals with JIA (106.2±95.781ng/ml vs. 182.24±108.428 ng/ml; p<0.01).

Conclusion: This study provides a further layer of evidence for the role played by IL-37 in JIA and creates new questions about the potential role of IL-38 in this condition.

KEYWORDS:
Juvenile idiopathic arthritis, IL-37, IL-38

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most prevalent rheumatic condition arising during childhood and adolescence.[1] JIA comprises a highly heterogeneous group of disorders, including systemic JIA (SJIA), which is characterised by a quotidian pattern of spiking fever, transient rash, as well as arthritis.[2] Patients with SJIA initially present with symptoms and signs seemingly non-specific to JIA, most likely owing to the syndrome's tendency to alternate between inactive and active (flare) periods.[1,2] SJIA was recently re-evaluated as an autoinflammatory syndrome rather than an autoimmune disease in keeping with the majority of rheumatic conditions.[3,4] Thus, in view of its heterogeneity, the diagnosis of JIA can be a challenge for professionals. Although it is impossible to draw conclusions relating to all JIA categories, owing to its elusive nature, SJIA is perhaps the best subgroup to study as it hypothetically allows for the identification of biomarkers that are specifically responsible for associated symptoms. Additionally, its re-classification as an autoinflammatory disease provides further excellent targets for future research strategies, most notably including the use of inflammatory biomarkers for the diagnosis and management of JIA.[1]

Some evidence, such as that arising from gene expression studies, has already demonstrated an existing link between the pathogenesis of SJIA and the balance of pro- and anti-inflammatory cytokines.[5] This is likely to reflect their involvement in systemic inflammation and joint damage, which are amongst the symptoms present in SJIA. Of these cytokines, the interleukins (IL), IL-6 and IL-17, as well as tumour necrosis factor-α are members of the group of pro-inflammatory cytokines associated with SJIA pathogenesis as well as being significantly elevated in the serum of patients with SJIA.[2,6,7] Furthermore, therapeutic targeting of these cytokines has been shown to cause less severe symptoms.[8] As such, these cytokines are useful when looking to diagnose and manage SJIA in active periods. However, since SJIA can often be sporadic in nature, the identification of specific cytokines that can be used as biomarkers for the purpose of managing the syndrome is also necessary. Additionally, the pro-inflammatory cytokines are often related to other diseases presenting with inflamed tissue; identifying biomarkers specific to SJIA is necessary.

One of the most potentially relevant cytokines in SJIA is IL-37,[9] which belongs to the IL-1 cytokine family.10 IL-37 is an anti-inflammatory cytokine that acts to reduce pro-inflammatory cytokine expression in several inflammatory diseases, including ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and adult-onset Still's disease (AOSD).[10,11] Although in healthy subjects the levels of IL-37 and IL-37 mRNA are both low, their expression in inflamed tissues and cells is markedly raised.[11,12] This occurs owing to the presence of increased levels of pro-inflammatory cytokines that stimulate IL-37 production. Moreover, IL-37 mRNA is significantly more stable in patients with inflammatory diseases, suggesting that IL-37 participates in the suppression of an excessive immune response. In pathologies such as JIA, it would be expected that IL-37 remains elevated and could therefore function as a reliable biomarker. There is some in vitro evidence to demonstrate that IL-37 inhibits the production of pro-inflammatory cytokines in peripheral blood monocytes

This article was accepted: 07 May 2022
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from individuals with SLE, RA, AS, and AOSD. The initial data are promising, as levels of IL-37 are correlated with the titres of pro-inflammatory cytokines in the serum of SJIA patients. It is also clear that IL-37 levels are higher in SJIA patients compared to those in healthy individuals.[9,13]

IL-38 is another lesser-known member of the IL-1 family, which has been recently discovered and characterised.[14,15] Owing to its novelty, little is known about this cytokine. Although it is essentially an anti-inflammatory mediator, in a similar manner to many cytokines, it may also function to upregulate other cytokines, such as IL-6. Currently, there is no link between IL-38 and SJIA. However, such a connection could be hypothesised as there is evidence suggesting an association with the adult-onset version of JIA, AOSD, indirectly through IL-36R,[15] which is one of the binding partners of IL-38.[10] Furthermore, in SLE, as with IL-37, higher levels of IL-38 are also detected in the blood of patients compared to healthy subjects.[10]

When this evidence is taken into account, a notable gap of knowledge in this field is the role of IL-38 in JIA. Thus, by attempting to replicate evidence surrounding the use of IL-37 as an inflammatory biomarker, this study aims to evaluate and consider the consistency of the roles of both IL-37 and IL-38 in children with JIA. Whilst confirming previous findings across JIA subgroups, a further objective is to provide novel evidence surrounding the part played by IL-38 in JIA.

MATERIALS AND METHODS

Sixty JIA patients fulfilling the International League of Associations for Rheumatology[16] classification criteria for JIA, who were referred to the rheumatology clinic at Baghdad Teaching Hospital and diagnosed by consultant rheumatologists, were recruited into this study. Additionally, 90 healthy age- and sex-matched control subjects were conscripted from healthcare units in Baghdad; their health status was ascertained based on a clinical evaluation by physicians.

All patients were assessed using the juvenile arthritis disease activity score-27.[17] Laboratory tests, including C-reactive protein (CRP) and rheumatoid factor (RF), were carried out for all subjects. Slide agglutination tests were used for the qualitative assessments of CRP (CRP-Latex, Spinreact Spain; Ref. ID: 1200305) and RF (RF-Immuno-Latex, La Wama Diagnostica, Brazil; Ref. ID: 28100-L).

IL-37 and IL-38 serum levels were measured by enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer instructions (MyBioSource, USA; Catalogue Numbers: RDEEH1120 (IL-37) and RDEEH14717 (IL-38)).

This research study has been approved by the Scientific Ethical Committee of the College of Medicine, University of Baghdad. All subjects' guardians gave informed consent according to the 2008 Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (version 21; SPSS, IBM). An independent samples' Student's *t*-test was employed for comparisons of quantitative variables between the studied groups, i.e., age/year and serum IL-37 and IL-38 levels. Data in a normal distribution were expressed as mean ± standard deviation. A Pearson chi-square test (χ^2) was used for comparisons of the qualitative variables between studied groups, i.e., age groups/year and gender. A binomial Z test was applied for RF and CRP assays. Data were given as (number) percentage. Finally, the validity of the ELISA test was estimated using the following parameters: ROC curve; cut-off value; area under curve (AUC); sensitivity (true positive) (%); specificity (true negative) (%); positive predictive value (PPV) (%); negative predictive value (NPV) (%); and accuracy (%). A *p*-value <0.05 was deemed statistically significant.

RESULTS

Sixty patients with JIA were recruited in the current study, i.e., 19 (31.7%) males and 41 (68.3%) females. Their ages ranged from 1 to 17 years, with a mean of 10.37±4.21 years. Additionally, 90 healthy persons were included as controls, i.e., 35 (38.9%) males and 55 (61.1%) females, with ages ranging from 3 to 19 years; mean age was 11.13±3.84 years. Evaluation of the groups' demographics showed that there were no differences between the subjects with JIA and the control group. The demographic data for the two cohorts are presented in Table I.

In patients with JIA, 42 (70%) were seronegative for RF and 18 (30%) were seropositive ($p<0.01$). The number of patients with negative and positive CRP levels were equivalent, i.e., 26 (45.33%) and 34 (56.67%), respectively (Table II).

When the distribution of positive and negative assays for CRP and RF, respectively, were compared within the varying demographic groups, no differences were seen (Tables III and IV).

The only exception was in those patients who were seronegative for RF, where a higher proportion of females compared to males was noted, i.e., 34 (78.05%) versus 9 (21.95%) ($p<0.05$) (Table IV). An equivalent distribution of RF seropositivity was noted between the sexes.

Compared to controls, serum IL-37 levels were increased in patients with JIA (117.98±209.282ng/ml vs. 37.87±24.496ng/ml; $p<0.001$), whereas serum IL-38 titres were diminished in individuals with JIA (106.2±95.781 ng/ml vs. 182.24±108.428 ng/ml) (Table V).

A positive correlation between serum IL-37 and IL-38 levels was demonstrated (r=0.633, *p*-value <0.001). In contrast, no correlation was identified between patients' age/year and either serum IL-37 levels (r=0.099, *p*-value =0.454) or IL-38 concentrations (r=0.021, *p*-value =0.88).

Validity of tests

The validity of the tests for serum IL-37 and IL-38 titres relating to their potential value for the diagnosis of JIA was assessed. For serum IL-37, the following parameters were obtained: cut-off value, 31.2 ng/ml; AUC, 0.549; sensitivity,

Table I: Demographic data for study groups: patients with juvenile idiopathic arthritis versus controls

Demographics		Control, n=90	Patient, n=60	*p*-value
Age / Year, Mean±SD	11.13±3.84	10.37±4.21	0.251	
Age groups / Year, n (%)	1–5	16 (17.8%)	8 (13.3%)	0.389
	6–10	43 (47.8%)	24 (40%)	
	11–15	22 (24.4%)	17 (28.3%)	
	16–20	9 (10%)	11 (18.3%)	
Gender, n (%)	Male	35 (38.9%)	19 (31.7%)	0.367
	Female	55 (61.1%)	41 (68.3%)	

Table II: Distribution of rheumatoid factor (RF) and C-reactive protein (CRP) amongst patients with juvenile idiopathic arthritis

		Patient, n=60		
Assay		N	%	*p*-value
CRP	Negative	26	43.33	0.366
	Positive	34	56.67	
RF	Negative	42	70	0.003
	Positive	18	30	

Table III: Distribution of C-reactive protein (CRP) amongst patients (n=60) with juvenile idiopathic arthritis: comparison of demographic data

Demographics		CRP		*p*-value
		Negative, n=42	Positive, n=18	
Age (Year), Mean±SD		10.50±4.052	10.26±4.385	0.832
Age groups (Year), n (%)	1–5	2 (7.7%)	6 (17.6%)	0.664
	6–10	12 (46.2%)	12 (35.3%)	
	11–15	7 (26.9%)	10 (29.4%)	
	16–20	5 (19.2%)	6 (17.6%)	
Gender, n (%)	Male	9 (34.6%)	10 (29.4%)	0.668
	Female	17 (65.4%)	24 (70.6%)	

Table IV: Distribution of rheumatoid factor (RF) amongst patients (n=60) with juvenile idiopathic arthritis: comparison of demographic data

Demographics		RF assay		*p*-value
		Negative, n=42	Positive, n=18	
Age (Year), mean±SD		10.57±4.162	9.89±4.404	0.569
Age groups (Year), n (%)	1–5	5 (11.9%)	3 (16.7%)	0.869
	6–10	16 (38.1%)	8 (44.4%)	
	11–15	13 (31%)	4 (22.2%)	
	16–20	8 (19%)	3 (16.7%)	
Gender, n (%)	Male	9 (21.95%)	9 (50%)	0.046
	Female	32 (78.05%)	9 (50%)	

Table V: Mean distribution of serum IL-37 and IL-38 levels amongst patients with juvenile idiopathic arthritis and controls and rheumatoid factor (RF) and C-reactive protein (CRP) assay results

Parameters		n	IL-37 (ng/ml)		IL-38 (ng/ml)	
			Mean±SD	*p*-value	Mean±SD	*p*-value
Study groups	Control	90	37.87±24.496	<0.001	182.24±108.428	<0.001
	Patient	60	117.98±209.282		106.20±95.781	
CRP assay	Negative	26	129.67±209.388	0.709	96.49±82.120	0.497
	Positive	34	109.04±211.903		113.61±105.651	
RF assay	Negative	42	98.20±158.040	0.267	112.08±103.094	0.472
	Positive	18	164.15±297.567		92.47±76.949	

55 %; specificity, 47.8%; PPV, 41.2%; NPV, 61.4%; and accuracy, 50.67%. These values failed to reach significance, (p=0.31).

For serum IL-38, the following parameters were obtained: cut-off value, 95.56 ng/ml; AUC, 0.749; sensitivity, 61.7 %; specificity, 67.8%; PPV, 56.1%; NPV, 72.6%; and accuracy, 65.34% (p-value <0.001).

DISCUSSION

Since JIA is an autoinflammatory condition, the roles of inflammatory and anti-inflammatory cytokines in this pathology are undisputed.[18] Amongst the key anti-inflammatory cytokines involved in the downregulation of inflammation in JIA is IL-37, whilst the function of its close and recently discovered family member, IL-38, remains unclear. Thus, the aim of this study was to confirm previous findings that described the role of IL-37 in patients with JIA as well as to investigate the role of IL-38 in this condition.

Demographic analysis of the study participants showed no significant differences in either age or gender between control and patient groups, thus indicating a high degree of subject matching. Analysis of CRP and RF status amongst the 60 patients with JIA revealed an equal distribution of patients between the CRP-positive and the CRP-negative groups. However, an uneven distribution of patients amongst the RF-positive and RF-negative groups was observed, with 70% of JIA patients exhibiting a negative RF status. Such results are consistent with the literature, which shows that most subtypes of JIA are RF-negative.19 Polyarticular JIA is the exception and can be either RF-positive or RF-negative.[19]

Demographic analysis of the JIA patient group according to RF status demonstrated that almost 80% of RF-negative patients were females, compared to the RF-positive group, in which the gender distribution was equal. This is in contrast to previous studies, which have shown that RF positivity is more common amongst females with JIA and, particularly, amongst those with polyarticular JIA.[19,20]

In line with previous evidence describing a key role of IL-37 in JIA, the current analysis revealed significantly higher levels of IL-37 in the JIA patient group compared to the controls, thus confirming previous findings.[13] More specifically, IL-37 has been shown to have an immunosuppressive function, mediated by the inhibition of inflammatory cytokine production.[9]

Although the levels of IL-37 expression were in line with the present hypothesis, results from this study demonstrated that the titres of IL-38, a recently discovered cytokine belonging to the IL-1-family, were significantly higher in the control group. This result is unexpected as previous study has shown that titres of IL-38 were increased in patients with autoinflammatory diseases, such as RA[21] and SLE.[22] Given the similar biological mechanisms underlying RA and JIA, the hypothesis that IL-38 may differ seems unlikely. However, there is some evidence that cytokine expression profiles differ between adult RA and JIA.[23] Thus, future study should aim to repeat the current experiment to ensure that no experimental shortcomings have interfered with the results. Furthermore, given the high levels of IL-38 in the control cohort, special attention should be paid to the possibility of higher-than-average levels of IL-38 amongst these patients, which could be owing to potentially undiagnosed conditions or the presence of outlier values. No significant differences were observed between the levels of IL-37 or IL-38, or between the CRP-negative and CRP-positive groups, or between the RF-negative and RF-positive cohorts, which may suggest the absence of a relationship between these factors.

In the patients with JIA, a strong positive correlation was revealed between the levels of IL-37 and IL-38. Although further study would have to be carried out to confirm this hypothesis, this finding could point towards a biological relationship between both interleukins in JIA. However, given the observation that IL-38 levels were significantly higher than IL-37 titres in control patients, it is likely that the positive correlation between IL-37 and IL-38 is only true in the context of JIA.

Finally, the suitability of IL-37 and IL-38 measurements to aid in the diagnosis of patients with JIA was analysed. A low specificity and sensitivity for IL-37 was obtained, together with an AUC of 0.549, indicating poor discrimination. Although the results for IL-38 revealed a good specificity and sensitivity, with an AUC of 0.749, the lower-than-expected levels of IL-38 in patients with JIA compared to healthy controls suggest the need for future validation of the role of IL-38 in JIA before its diagnostic utility can be determined.

CONCLUSION

This study provides another layer of evidence relating to the role played by IL-37 in JIA and creates new questions regarding the potential role of IL-38 in this condition.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

FUNDING STATEMENT

This research article was entirely funded by the author.

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ORIGINAL ARTICLE

Development and validation of Malaysian noise and chemical exposure questionnaire towards hearing among hospital workers

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ABSTRACT

Introduction: Questionnaire is one of the effective, easy, and quick preliminary tools, which is widely used in today's healthcare assessment. It is important to have a suitable questionnaire according to the target population and also one that is culturally appropriate based on the intended countries' laws and regulations. The objective of the study is to develop and validate a Malaysian version of noise and chemical exposure questionnaire.

Materials and Methods: The questionnaire was developed and validated by experts and undergone a viability pilot study that involved a total of 60 workers, divided into two groups, 30 workers for the non-exposed (control group) and 30 workers who were exposed (target group) to both noise and chemicals in their workplace. The workers were recruited from a hospital in Kuantan, Pahang. The workers were requested to complete the Malaysian version of the questionnaire, disseminated through email and the WhatsApp platform.

Results: The final questionnaire consisted of 62 items, which was reviewed by experts. The validity process of the internal consistency showed good reliability, with a Cronbach's alpha of 0.76 and Pearson Correlation of r=0.638, ρ<0.01. The null hypothesis is rejected, there is an association between workers working at high risk workplace and risk of developing chemical-induced hearing loss. Thus, questionnaire can serve as a preliminary tool to select workers with a significant exposure for further evaluation.

Conclusion: The noise and chemical exposure questionnaire is valid and suitable to be used in Malaysia as it is in the native Malay language and abides by the culture, laws, and regulation of the country.

KEYWORDS:
Malaysia; hearing loss; chemical exposure; noise; questionnaire

INTRODUCTION

Application of the preliminary tools as an early assessment in the healthcare field is important to prevent further unnecessary evaluation as it can be seen as less time consuming, low to no cost, and can be used to generate a large amount of data. The same scenario is applicable for the assessment of noise-induced hearing loss (NIHL) and chemical-induced hearing loss (CIHL) among industrial workers. It is widely known that occupational hearing loss had been a major economic burden around the world. Several guidelines and regulations had been introduced in Malaysia by Ministry of Human Resources, Department of Occupational Safety and Health in 2022 such as the Occupational Safety and Health (Noise Exposure) Regulation 2019, Industry Code of Practice for Management of Occupational Noise Exposure and Hearing Conservation 2019, Guidelines on Management of Occupational Noise Related Hearing Disorders and safety data sheets (SDS) for the chemical exposure.[1]

Chemical hazard has been identified to cause hearing loss; specifically, organic solvents together with the presence of noise had been found to induce a synergistic oto-traumatic effect on the auditory function worse than the exposure to noise and solvents alone.[2] Since it has been widely known that solvents and noise co-exist in many industrial sectors, attention has been shifted towards finding audiological tools that are effective in detecting the ototoxicity effects of the solvent exposure. It is established that audiological assessments are the main tools in the diagnosis of hearing loss, but the inclusion of preliminary tools, such as questionnaires and pre-examination, is what is needed for the assessor to get an early impression of what to expect.

Assessment of the effects of noise exposure has already been established with pure-tone audiometry; however, the effect of chemical exposure is still under research. The organic solvent study conducted by Sliwinska-Kowalska et al.,[3] Liu et al.,[4] and Kaufman et al.[5] included detailed inquiries about the present and previous exposure to solvents and noise, medical history, and non-occupational exposure to ototoxic agents. The medical history questions inquired about signs and symptoms relating to the auditory system include and not limited to history of middle-ear diseases and surgery, hereditary disorders, chronic systemic diseases, cholesterol level and hypertension, head trauma, and current and past medications containing potential ototoxic agents. Another research by Fuente et al., also used a medical and

This article was accepted: 07 May 2022
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occupational history questionnaire to filter out the participants with the pre-existing medical conditions associated with hearing and a participant's noise exposure level based on their observations.[6]

Currently, there are several noise and chemical questionnaires available, although none is specific to the Malaysian population. The recently enacted Noise Regulation 2019 had enforced the need to fill a hearing-related questionnaire in Industry Code of Practice for Management of Occupational Noise Exposure and Hearing Conservation 2019 in every audiometric testing conducted. Alas, the chemical-related questions were not included, which prompted Yusof et al.[7] to use the adapted noise and chemical (NOISECHEM) questionnaire developed by Prasher et. al.[8] to screen for the prevalence of CIHL in Malaysia. Looking at the NOISECHEM adaptation, we felt there is a need for a local version of this questionnaire, which became the main objective of the study, that is, to develop a Malaysian noise and chemical exposure questionnaire for our workers, which is appropriate to the culture, laws, and regulations of our country.

MATERIALS AND METHODS

Development of Questionnaire

Firstly, literature reviews related to both noise and chemical exposure were conducted through online search platforms such as Google Scholar, PubMed, and Medline. The search for available questionnaire regarding the exposure agents had also been carried out to search for the focus items and question that is often being asked in the intended survey. A focus group discussion with three experts from audiology, and occupational safety and health were conducted to gain insight into the details for the question and addition of a few items.

To assess both exposures to noise and chemicals, the questionnaire was divided into four domains. Firstly, demographic data (eight items) on each of the respondents such as age, gender, race, and educational level were included. Secondly, we assessed the risk of developing NIHL, which depends on two parameters of sound levels, i.e., duration of time, and level of intensity.[9] For the assessment of the chemical exposure, a column was prepared for those who are aware of what types of chemicals they are exposed to. Additionally, activities involving chemicals were also included considering some workers may not know the name of chemicals that they are exposed to. Other parameters include duration and chemical exposure levels. Responses are towards open-ended and multiple-choice questions with a varied number of responses. Three native Malay speakers fluent in both English and Malay had been chosen to assess the correct semantical and grammatical use of the languages in the questionnaire.

Validation of Questionnaire

Three versions of the questionnaire were reviewed through focus group discussions which included an audiologist from Audiology unit, Sultan Ahmad Shah Medical Centre (SASMEC), audiological medicine doctor from Ear & Hearing Clinic, Kulliyyah of Medicine, and occupational health doctor from Kulliyyah of Allied Health Sciences, both are from International Islamic University of Malaysia before the final draft of the questionnaire was produced and sent to other experts from other institutions for validation purposes. The content validation process of the Malaysian noise and chemical questionnaire was assessed by experts in various fields, i.e., Industrial Audiology, Audiological Medicine, and Occupational Health, to check for the degree of relevancy and appropriate representativeness of each item on the questionnaire and the item content validity indices (I-CVIs), and multi-rater kappa statistics were calculated. For the face validity, the review experts represented their subjective opinion for the assessment items to see whether it is appropriate to the targeted construct and objectives of the questionnaire based on the feasibility, readability, and clarity of the language used. Then, the construct validity of the questionnaire was obtained through a statistical analysis of inter-reliability of Cronbach's alpha and Pearson correlation coefficient.

Reliability of Questionnaire

Reliability of the questionnaire was determined through internal consistency analysis using Cronbach's alpha, a function of the average intercorrelations of items and the number of items in the scale. The internal consistency of 0.7 and more indicated a good internal consistency.[10] Then, for the feasibility analysis, a pilot study was conducted to identify potential problem areas and deficiencies in the research instruments and protocol before implementation during the full study.[11,12] The potentially exposed workers had been selected for the study at a hospital in Kuantan, Pahang. Selected respondents were categorised into a control and exposed group. Before the selection, permission was sought both from the individual respondent and their head of department. Workers exposed to organic solvents and noise with a total of 60 respondents volunteering to participate in the research. Primarily, targeted sampling methods were used to categorise the respondents' group according to their workplace of no exposure and exposure to noise and chemical. Then, the respondents' percentages of answer rate of 'YES' to the selected items associated with the chemical and noise exposure were reviewed to categorise them into the final group of exposure, 60% of 'YES' answer and non-exposure, 40% of 'YES' answer. Descriptive analyses were used to analyse the demographic data such as age, gender, and educational level. The data were analysed using IBM SPSS Statistics 24.

RESULTS

Validation of Questionnaire

The face and content of the questionnaire were validated by experts in Industrial Audiology, Occupational Medicine, and Audiological Medicine with a total of five experts: one from Industrial Audiology, one from Audiological Medicine, and three from Occupational Medicine. The panel experts have given their opinion and comment regarding the face validity, and their ideas were revised and incorporated in the questionnaire accordingly. However, for the content validity, the evaluation was conducted using a Likert scale of five intervals (1 – not relevant, 2 – not quite relevant, 3 – quite relevant, 4 – relevant, 5 – strongly relevant) to check for the

Table I: Calculation of I-CVIs of expert evaluation

No	Items	Relevant (rating of 3,4, or 5)	Not relevant (rating of 1 or 2)	I-CVIs	Interpretation
1	Job title and working unit	4	1	0.8	Appropriate
2	Specific task	5	0	1	Appropriate
3	Years and months of working	5	0	1	Appropriate
4	Days and hours of working	5	0	1	Appropriate
5	The current workplace noise level	4	1	0.8	Appropriate
6	Wearing of personal hearing protection and its type	4	1	0.8	Appropriate
7	Use of noisy powered tools or machinery	4	1	0.8	Appropriate
8	At your current workplace, is there a warning sign of excessive noise?	4	1	0.8	Appropriate
9	At work, do you need to yell or raise a voice with someone 1 meter away?	4	1	0.8	Appropriate
10	After work, do you experience a change in hearing or ability to understand speech? If yes, which ear?	4	1	0.8	Appropriate
11	After work, do you feel ringing or humming in the ear? If yes, which ear and its frequency?	4	1	0.8	Appropriate
12	Previously, do you work in a noisy workplace?	5	0	1	Appropriate
13	How long have you worked there?	5	0	1	Appropriate
14	Do you wear a personal hearing protector and its type?	4	1	0.8	Appropriate
15	Are you exposed to chemicals in the current workplace?	4	1	0.8	Appropriate
16	At the current workplace, do you use pesticides or herbicides?	4	1	0.8	Appropriate
17	At the current workplace, do you use harsh chemicals (varnish, glue, acid)?	4	1	0.8	Appropriate
18	At the current workplace, do you do welding or soldering?	4	1	0.8	Appropriate
19	At the current workplace, do you use metals (lead, mercury, etc.)?	4	1	0.8	Appropriate
20	At the current workplace, do you use to paint?	4	1	0.8	Appropriate
21	At the current workplace, do you use cleaning chemicals?	4	1	0.8	Appropriate
22	If there is a usage of the above materials or activities, state how many hours per day, days per week, and years of exposure.	4	1	0.8	Appropriate
23	Are you exposed to the materials or activities above previously?	4	1	0.8	Appropriate
24	If yes, state the name of materials or activities, how many hours per day, days per week, and years of exposure.	4	1	0.8	Appropriate
25	Does your current workplace smell uncomfortable and pungent?	4	1	0.8	Appropriate
26	Do you experience headache or dizziness caused by the pungent smell?	4	1	0.8	Appropriate
27	Do you feel your headache or dizziness getting better over the weekend?	4	1	0.8	Appropriate
28	Are you wearing protective equipment such as a glove, apron, and respirator? If yes, please state the type.	5	0	1	Appropriate
29	Current hearing level (right and left)	4	1	0.8	Appropriate
30	If not good, how long have you had the hearing problem?	4	1	0.8	Appropriate
31	Have you had any disease or problem related to ear or hearing since childhood until now? If yes, please state the name of the disease.	4	1	0.8	Appropriate
32	Have you ever had measles?	3	2	0.6	Eliminated
33	Have you ever had hypertension?	2	3	0.4	Eliminated
34	Have you ever had tuberculosis?	3	2	0.6	Eliminated
35	Have you ever had diabetes?	3	2	0.6	Eliminated
36	Have you ever had mumps?	3	2	0.6	Eliminated
37	If you ever had any disease above; state for how long, medication taken, and any effect on hearing.	3	2	0.6	Eliminated

Table I: Calculation of I-CVIs of expert evaluation (con't)

No	Items	Relevant (rating of 3,4, or 5)	Not relevant (rating of 1 or 2)	I-CVIs	Interpretation
38	Have you ever experienced any head injury and loss of consciousness? If yes, which ear, when, and further explanation?	5	0	1	Appropriate
39	Have you ever had an explosion that caused hearing problems? If yes, which ear, when, and further explanation?	4	1	0.8	Appropriate
40	Have you ever had ear surgery? If yes, which ear, when, and further explanation?	4	1	0.8	Appropriate
41	Are there any family members who have had hearing problems since childhood? If yes, who?	4	1	0.8	Appropriate
42	Do you have tinnitus (ringing or buzzing in the ears)?	4	1	0.8	Appropriate
43	If yes, which ear and its frequency?	4	1	0.8	Appropriate
44	Do you smoke or vape?	4	1	0.8	Appropriate
45	If yes, for how long and how many cigarettes or vapes per day?	4	1	0.8	Appropriate
46	If not, are there family members or friends who smoke or vape and live in the same house as you?	4	1	0.8	Appropriate
47	Do you consume liquor or alcohol?	4	1	0.8	Appropriate
48	If yes, state the frequency.	4	1	0.8	Appropriate
49	Have you been doing woodworking?	4	1	0.8	Appropriate
50	Have you been doing metalworking	4	1	0.8	Appropriate
51	Have you ever used heavy equipment?	2	3	0.4	Eliminated
52	Have you ever used a chain saw?	4	1	0.8	Appropriate
53	Have you ever used grinders or chippers?	4	1	0.8	Appropriate
54	Have you ever used air-driven tools?	4	1	0.8	Appropriate
55	Have you ever done motorsports?	4	1	0.8	Appropriate
56	Have you ever done farming?	4	1	0.8	Appropriate
57	Have you ever boarded a plane?	2	3	0.4	Eliminated
58	Have you ever played music (musical instruments, headphones, etc.)?	5	0	1	Appropriate
59	Have you ever used a firearm?	5	0	1	Appropriate
60	Have you ever used a leaf blower or trimmer?	2	3	0.4	Eliminated
61	Have you ever visited an entertainment centre (karaoke, concerts)?	2	3	0.4	Eliminated
62	If you did the above activity, state the duration of exposure and whether you wore hearing protection during the activity.	4	1	0.8	Appropriate

Table II: Frequency of the percentage of answer 'YES' of respondents in the questionnaire

Percentage (%) of answer 'YES'	Frequency
0	3
10	4
20	4
30	6
40	7
50	6
60	2
70	8
80	13
90	7
100	0

relevancy and clarity of each item. The Likert data were then calculated for content validity index for relevancy and clarity of each item (I-CVIs), and the score of each item set as relevant or clear (a rating of 3, 4, or 5) was divided by the number of content experts. The analysis of the five-point Likert scale is as follows.

From Table I, judgement on each item was made as follows: If the I-CVI is higher than 79%, the item will be appropriate. If it is between 70% and 79%, it needs revision. If it is less than 70%, it is eliminated.[13]

The result showed that 52 out of 62 items had a score of 79 percent and above, signifying the majority of the items put forth is relevant and appropriate. The 10 items scoring below 70% were considered for elimination. Prior to that, the items were re-evaluated accordingly. Subsequently, four items were deleted, one item was changed, and five items maintained as

Table III: Demographic characteristics of participants

Group		Control		Exposure	
Socio-demographic variable		**Frequency (n=30)**	**Percentage (%)**	**Frequency (n=30)**	**Percentage (%)**
Age (year)	20-29	16	53.3	18	60.0
	30-39	11	36.7	11	36.7
	40-49	0	0.0	1	3.3
	50-59	3	10.0	0	0.0
Gender	Males	14	46.7	8	26.7
	Females	16	53.3	22	73.3
Educational level	SPM	6	20.0	0	0.0
	STPM/Diploma	11	36.7	14	46.7
	Bachelor's degree	11	36.7	13	43.3
	Master's degree	1	3.3	3	10.0
	Ph.D.	1	3.3	0	0.0

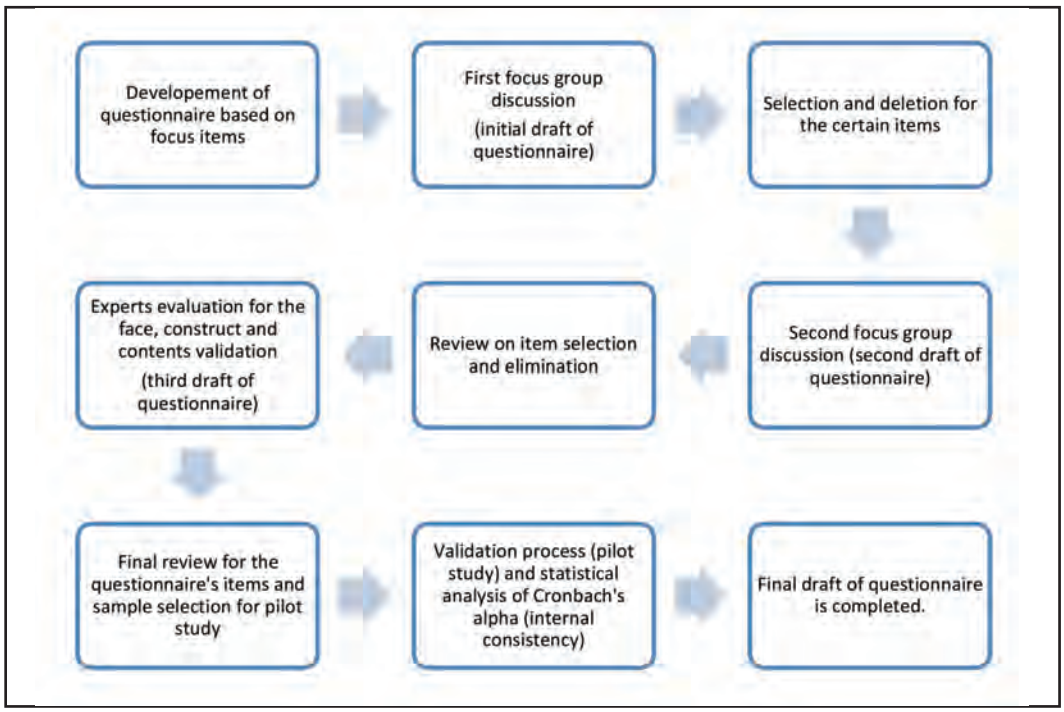

Fig. 1: Flowchart of the development process of Malaysian Noise and Chemical Exposure Questionnaire

we felt their association with the hearing condition is well established and it serves as an additional information for the researchers.

The multi-rater kappa statistics were calculated for chance of agreement through IBM SPSS Statistic 24 software. Kappa values above 0.74, between 0.60 and 0.74, and between 0.40 and 0.59 are considered as excellent, good, and fair, respectively. The result for the kappa analysis is 0.68, which therefore can be considered as good.

For the non-occupational section, confusion may arise from the usage of the words. For example, music can be playing a musical instrument or listening to music through headphones or a speaker. Thus, we have included an example for the music exposure, which included both playing musical instruments and listening to music via headphones. These misunderstandings can be minimised if the mode of administration is through an interview session instead of self-administered.

Pilot Study for Viability of Questionnaire

After the development and validation of the questionnaire, we proceeded with viability analysis through a pilot study that involved a group of workers from a tertiary hospital in Kuantan, Pahang. The validated questionnaire was disseminated through WhatsApp and email platform to 60 respondents, where 30 were selected from office workers categorised into the control group (non-exposed) and 30 respondents from the lab and pharmacy department who were put into the exposed group. The criteria selection for respondents in the exposed group are based on items related to noise exposure (items 5-12) and chemical exposure (items 15-21, 23, 25-27). Respondents with a 60% answer rate of 'YES' to the intended items are categorised under the exposed group. Meanwhile, the remaining respondents, who self-claimed to have no-to-low exposure and answered 'NO' (40% answer rate) to the appropriate items, were categorised into the non-exposed or control group. In relation to the division of the respondents, we were able to distinguish the respondents using the questionnaire; the respondent's workstation tallied with our observation of no-to-low

occupational exposure, and similarly, the exposed group with high risk of hazardous chemical and noise exposure especially during working hours can also be identified via the questionnaire. Table II shows primary data of targeted sampling and categorisation based on the questionnaire.

The questionnaire was reported to take around 10 minutes to answer, and data collection had taken place from August 2021 until October 2021. The face-to-face method was minimised in view of the COVID-19 pandemic. The demographic data of the respondents are shown in Table III. Respondents randomly selected from the control group have a mean age of 30.80±8.39 years with no exposure to either noise or chemicals. Meanwhile, the designated target group has a mean age of 28.42±4.13 years selected from a specific department in the hospital known to be exposed to noise and chemicals at work.

The gender distribution of the respondents are 36.7% males and 63.3% females. For the educational level of the respondents; a majority of them had a diploma (41.7%), followed by a bachelor's degree (40.0%), SPM (10.0%), master's degree (6.7%), and one with Ph.D. qualification (1.7%). Additionally, 39 people (65.0%) had worked for at least three years in their position and throughout the week, and 43 of them (71.7%) need to work for five days a week. Forty-five people worked for eight hours per day, only 20.0% of them worked for more than eight hours, and the remaining 5.0% worked for less than normal working hours.

The 60 respondents were also asked to include their opinions regarding the clarity of the language used and overall comprehensiveness of the questionnaire. From this, we have identified a few items that are quite difficult to understand. One example is the amount of exposure where the respondents could not recall the exact exposure duration. The respondents' subjective opinion regarding the face validity, however, did not result in major changes to the questionnaire as these items could not be avoided to ensure the questionnaire is able to cover all possible information regarding noise and chemical exposure.

Construct validity was assessed firstly through the inter-reliability of the questionnaire via the analysis of Cronbach's alpha. The reliability of 62 items in the questionnaire had been calculated using SPSS, and the score was 0.76, which indicated a good internal consistency. Another method for assessing construct validity is through Pearson correlation coefficient. The general null hypothesis (H_0) and alternative hypothesis (H_1) of the significance test for correlation of two-tailed test are H0: $\rho=0$ ('There is no association between workers working at high risk workplace and risk of developing chemical-induced hearing loss'), and H1: $\rho\neq0$ ('There is an association between workers working at high risk workplace and risk of developing chemical-induced hearing loss'). From the correlation coefficient, between workers working at high-risk workplace and risk of developing chemical-induced hearing loss, a statistically significant linear relationship ($r=0.638$, $p<0.01$) was found. Workers at high-risk workplace and at risk of developing chemical-induced hearing loss are positively correlated, whereas workers at high-risk workstation are associated with greater risk of developing a hearing loss due to the chemical exposure. The magnitude, or strength, of the association is considered moderately correlated ($0.5< | r | <0.7$). Thus, the null hypothesis, where $\rho\neq0$, is rejected.

DISCUSSION

The feedback from respondents during the validation process compelled us to administer the questionnaire through interview session instead of self-administration. This is to ensure the answers for the questionnaire are aligned to the objectives of the questionnaire development. Additionally, the face, content, and construct validity were obtained and refined, which further improved the questionnaire's overall validity. The questions are now more technically accurate and can provide more detailed information about respondents' risk of developing early hearing impairment due to the presence of noise and chemical exposure.

Available noise and chemical (NOISECHEM) questionnaire from the previous study by Prasher et al.[8] included items such as eye and skin colour. Differences in the features are not prominent in Malaysia compared to Westerners, which is why we excluded them. They also included items for alcohol and drug intake, which can be considered as culturally insensitive queries here in Malaysia. Thus, we had omitted those items as well during the development of the questionnaire.

Previous study by Cabello-López et al.[14] reported that it is hard to estimate a single chemical exposure when mixtures of chemicals were involved. Cabello-López et al.[14] also stated the need to include a more accurate exposure modelling for specific elements due to a lack of details of exposure histories and current exposure levels. It has become crucial for researchers studying the same field to sought for more specific details of the exposure indirectly from the activities related to the chemicals instead of the name of a specific chemical. This is justified by the fact that workers usually do not know the scientific term of the chemicals and will use only layperson terms to describe it, which can also lead to inaccurate interpretation.

The advantage of this questionnaire is that it covers all aspects of hearing loss either exposed to noise or chemical, confounding factors, and exposure outside the workplace. This has saved the researchers a lot of time in determining any hearing or ear-related issues. Additionally, this is the first noise and chemical exposure questionnaire available for Malaysian population. We produced the questionnaire as an alternative assessment that conforms to our culture, laws, and regulations. Penafiel[9] in 2007, developed a noise exposure questionnaire for children, which highlighted the importance of using questionnaires as a useful tool for the screening of specific target population. Thus, the questionnaire is a cost-effective and time-saving assessment method preceding further audiological testing.

However, this study also comes with a few shortcomings. The mode of distribution for this questionnaire was via online platform, which was intended to be self-administered. A few significant items that require respondents' response could not

be properly obtained, which lead to recall bias. We felt that these non-responses could have been overcome had it been a personal interview. Additionally, accurate exposure data could not be obtained in the questionnaire where Fuente et al.[15] in 2013, and Mohammadi et al.[16] in 2010, also noted as a limitation in their studies. One of the alternative suggestions is to get the precise exposure data from a chemical health risk assessment conducted at the workplace. The items regarding exposure in the questionnaire are only to serve as an observation regarding the worker's self-awareness towards hazardous exposure.

The questionnaire was also able to categorise the workers into the exposed and non-exposed groups. This is according to the percentage of answer of 'YES' and 'NO' to the selected items regarding the noise and chemical exposure at the workplace, which will determine the group they belong to. Moreover, the non-occupational domain serves as additional data to the researchers on exposures outside of the workplace. The Malaysian Noise & Chemical Questionnaire is a screening tool to select workers who have been exposed to both noise and chemicals for further evaluation and diagnostic of hearing loss and not a measure to specific chemical exposure. Hence, the questionnaire serves its purpose as a preliminary tool to the audiological assessment in workers at risk of developing hearing loss from hazardous exposure to noise and chemical at work.

CONCLUSION

A reliable and valid questionnaire has been developed in this study, which enables one to assess knowledge and exposure to noise and chemical towards the hearing system, especially among the exposed workers. Although it needs further review and improvement, it can be used to identify workers at high risk of exposure to noise and chemical hazards and allow more detailed exposure monitoring followed by appropriate control measures.

FUNDING

The research was funded by Sultan Ahmad Shah Medical Center (SASMEC) @ International Islamic University Malaysia (IIUM); grant number SRG21-050-0050.

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Prevalence of abnormal cranial CT scan in nontraumatic headache patients with red flag symptoms at the emergency department in Hospital Universiti Sains Malaysia

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ABSTRACT

Introduction: Data on the prevalence of nontraumatic headaches with red flag symptoms in Asia are sparse. Therefore, the objectives of this study were to determine the final diagnosis and prevalence of abnormal CT scans in patients who presented to the emergency department (ED) with red flag symptoms.

Materials and Methods: This was a retrospective study based on the Radiology Department database of patients who presented to the ED with complaints of nontraumatic headache, had red flag symptoms, and underwent cranial CT scans. The inclusion criteria were adult patients presenting through the ED with nontraumatic headache who underwent cranial CT scans. Multivariate analysis was performed based on logistic regression to analyse the significance of the predictive value for abnormal CT scans.

Results: A total of 216 patients underwent cranial CT scans in the ED. More than half of the cases (53.7%) were male. A total of 146 patients (67.6%) had no obvious abnormalities in the CT scans, while 41 patients (19.0%) had cranial infarction, 9 patients (4.2%) had intracranial bleeding, and 20 patients (9.3%) had brain tumours. The most common diagnosis was primary headache syndrome, followed by cerebral vascular accident (CVA). Multivariate analysis showed that three factors were associated with abnormal CT scans: age, systolic blood pressure (SBP), and mean arterial pressure (MAP). New onset of headache at the age of 50 years or older (Odds Ration, OR 3.21, 95% Confidence Interval, CI 1.15, 8.94), SBP (OR 4.82. 95%CI 2.29, 10.40) and MAP (OR 6.21, 95%CI 2.71, 14.70) were significant.

Conclusion: The prevalence of abnormal CT scan findings in nontraumatic headache patients with red flag symptoms was 32%. Primary headache syndrome is the most common diagnosis. An age greater than 50 years old during the onset of headache, SBP greater than 180mmHg and MAP greater than 120mmHg were associated with a higher risk of abnormal cranial CT scans.

KEYWORDS:
nontraumatic headache, red flag symptoms, CT scan, emergency department

INTRODUCTION

Headache is a common presenting complaint in the emergency department (ED). It accounts for 1-4% of all ED visits.[1] Over time and centuries, the approaches to nontraumatic headache have become more systematic. Since 1992, the classification of headache by the International Headache Society has been incorporated into the 10th edition of the International Classification of Diseases (ICD-10) by the World Health Organization (WHO).[2] Based on the classification, all headache-related disorders are classified into three main classes: primary headaches, secondary headaches, and central neuralgias – central, primary facial pain, and other headaches.[3] Each class of headache contains explicit diagnostic criteria, and the specific meaning includes quantities rather than vague terms such as several or usually, which are based on clinical and laboratory observations.[4]

Deciding which adult patients have potentially life-threatening conditions can be challenging.[5] The term red flag was used to act as a screening tool to help identify headache patients who would benefit from urgent neuroimaging.[6,7] In 2003, 'SSNOOP' mnemonic (systemic symptoms/signs and disease, neurologic symptoms or signs, onset sudden or onset after the age of 40 years, and change of headache pattern) was introduced by Dodick to assist in identifying these symptoms.[8] Since then, many guidelines have provided more characteristics for the red flags, leading to the current SNNOOP10.[9]

Nevertheless, not all red flag symptoms are associated with abnormal computed tomography (CT) scan findings. For example, 80% of severe and rapid onset headaches have a final diagnosis of primary headache syndromes.[10] Another study in The Netherlands found that the number needed to scan to detect an intracranial cause of the headache was 7.6.[11] Some studies also revealed that most scans of headache patients with sinister features or red flag symptoms had low predictive value.[9,12] However, data on the final diagnosis of headache with red flag symptoms who presented through ED in Asia are sparse. Therefore, the objectives of this study were to determine the final diagnosis and prevalence of abnormal CT scans in patients who presented to the ED with 'SSNOOP' - red flag symptoms.

This article was accepted: 11 May 2022
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Table I: Demographic data and variable results collected (n=216)

Independent variables		Frequency (%)	Mean (SD)
Gender	Male	116 (53.7)	
	Female	100 (46.3)	
Race	Malay	213 (98.7)	
	Chinese	3 (1.3)	
Age			49.5 (±0.99)
SBP (mmHg)			151.97 (±1.2)
DBP (mmHg)			88.7 (±0.62)
MAP (mmHg)			109.83 (±0.70)
CT Scan Findings	No abnormality detected	146 (67.6)	
	Abnormal CT scan	70 (32.4)	
	• Infarction	41 (19.0)	
	• Bleeding	9 (4.2)	
	• Tumours	20 (9.3)	
Disposition	Admission to the ward	104 (48.1)	
	• Neuromedical	44 (20.4)	
	• Neurosurgical	30 (13.9)	
	• Otorhinolaryngology	8 (3.7)	
	• Ophthalmology	1 (0.5)	
	• Medical	19 (8.8)	
	Discharge	112 (51.9)	
	• Referral to specialist clinic	103 (34.2)	
	• General clinic referral	9 (4.2)	
Diagnosis given in ED	Primary HA syndrome	134 (62.5)	
	BPPV	7 (3.2)	
	Ischaemic stroke	41 (19.0)	
	Brain tumours	20 (9.3)	
	ICB group	9 (4.2)	
	• Intraparenchymal - 1		
	• Intraventricular - 4		
	• Epidural - 2		
	• Subarachnoid - 2		
	TIA	4 (1.8)	
	Viral Fever	1 (0.5)	

BPPV: Benign Postural Vertigo, CT: Computed Tomography, DBP: Diastolic Blood Pressure, HA: Headache, ICB: Intracerebral bleeding, MAP: Mean Atrial Pressure, SBP: Systolic Blood Pressure, SD: Standard Deviation, TIA: Transient Ischaemic Attack

Table II: Frequency table of ('SSNOOP') red flag symptoms in nontraumatic headache patients

Red flags symptoms*	Complaint	n (%)
Systemic symptoms	Fever	26 (12.0)
	Weight loses	2 (0.9)
Systemic disease	Infection	6 (2.8)
	HIV	4 (1.9)
	Suspect malignancy	2 (0.9)
Neurologic symptom	Generalised weakness	56 (25.9)
	Numbness	32 (14.8)
	AMS	33 (15.3)
	Seizures	16 (7.4)
	Severe Giddiness	87 (40.3)
	Visual disturbances	35 (16.2)
	Paralysis (limbs or facial)	68 (31.5)
Onset sudden (thunderclap headache)	Severe headache in life	78 (36.1)
Onset after age 40 years	First onset of headache	126 (58.3)
	Persistent vomiting with headache	79 (36.6)
Previous headache history (first, worst, or different headache)	New abnormal headache	61 (28.2)

*Based on patients' complaints and history. All of the patients had more than one complaint.
AMS: Altered mental status, HIV: Human immunodeficiency virus

Table III: Associated factors of patients with abnormal computed tomography (CT) scan by univariate logistic regression analysis and multivariate logistic regression

			Univariate analysis					Multivariate analysis		
		CT Normal n (%)	CT Abnormal n (%)	Fraction f (%)	OR	95% CI	*p*	OR	95% CI	*p*
Age	>50	146 (67.6)	70 (32.4)	216 (100)						
	<50	110 (50.9)	66 (30.5)	176 (81.4)	1	1.60, 6.13	0.001	3.21	1.15, 8.94	0.024
Gender	Male	36 (16.7)	4 (1.9)	40 (18.6)	3.13					
	Female	78 (36.1)	38 (17.6)	116 (53.7)	1	0.34, 1.22	0.170			
SBP	>180	68 (31.5)	32 (14.8)	100 (46.3)	0.64					
	<180	110 (50.9)	54 (25.3)	164 (76.2)	1	1.28, 6.52	0.010	4.82	2.29, 10.40	<0.001
DBP	>110	36 (16.7)	16 (7.1)	52 (23.8)	2.88					
	<110	125 (57.8)	60 (28.3)	185 (86.1)	1	0.90, 6.74	0.070			
MAP	>120	21 (9.3)	10 (4.6)	31 (13.9)	2.46					
	<120	113 (52.3)	55 (25.5)	168 (77.8)	1	1.09, 6.63	0.040	6.21	2.71, 14.70	<0.001
		33 (15.3)	15 (6.9)	48 (22.2)	2.67					

OR: odds ratio, CI: confidence interval, DBP: diastolic blood pressure, MAP: mean atrial pressure, SBP: systolic blood pressure

MATERIALS AND METHODS

This was a retrospective study based on the Radiology Department database of patients who presented to the ED with nontraumatic headache as one of the complaints, had red flag symptoms, and underwent cranial CT scans. The data were collected from 2009 to 2012 in Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia. The inclusion criteria were adult patients (more than 12 years old) presenting through the ED with nontraumatic headache who had either one or more red flag symptoms and underwent cranial CT scans. The exclusion criteria were any patient who was known to have any intracranial lesion and referred cases from district hospitals or clinics with suspected intracranial lesions. The cranial CT scan findings were categorised as normal findings or abnormal findings based on the report by the radiologist.

The data collection started from reviewing the database. The request for the CT scan must be made by the ED doctors of Hospital USM. From the database, case notes were traced. All cases were reviewed based on the inclusion and exclusion criteria. A format sheet was created for the documentation and data collection. Demographic data, vital signs, history taking documentation, physical examination findings, cranial CT scan findings, diagnosis, and disposition from the ED were recorded. The collected data and variables from the samples were categorised accordingly by statistical analyses using SPSS™ 22. Multivariate analysis was performed based on logistic regression to analyse the significance of the predictive value from the univariate analysis. Ethical approval was obtained from the Ethical Board Review and Hospital Ethics Committee on 29 July 2013 (Reference USMKK/PPP/JEPeM [270.4(1)]. The sample size was determined using the single proportion method and based on the prevalence of headache in a renowned international study by Goldstein et al., in 2006.[13] The power sample was significantly calculated with the value of 92 samples for this study.

RESULTS

A total of 216 patients who presented with red flag symptoms underwent cranial CT scans in the ED, Hospital USM. The flow of the study and number of patients distribution are summarised in Figure 1. More than half of the cases (53.7%) were male. The mean age was 49.5 (SD±0.99) years old, with the youngest patient being 16 years old and the oldest patient being 83 years old.

The mean systolic blood pressure (SBP) was 151.97mmHg (SD±1.2), and the diastolic blood pressure (DBP) was 88.7mmHg (SD±0.62), with a mean atrial pressure (MAP) of 109.83mmHg (SD±0.70). A total of 146 (67.6%) patients had no obvious abnormalities, 41 (19.0%) patients had cranial infarction, 9 (4.2%) patients had intracranial bleeding, and 20 (9.3%) patients had brain tumours. Details of the factors and diagnosis are presented in Table I.

Table II shows the most common 'SSNOOP' - red flag symptoms are the first onset of headache in a patient more than 40 years old. It accounted for 58.3% of all cases. The second and third most common red flag symptoms were

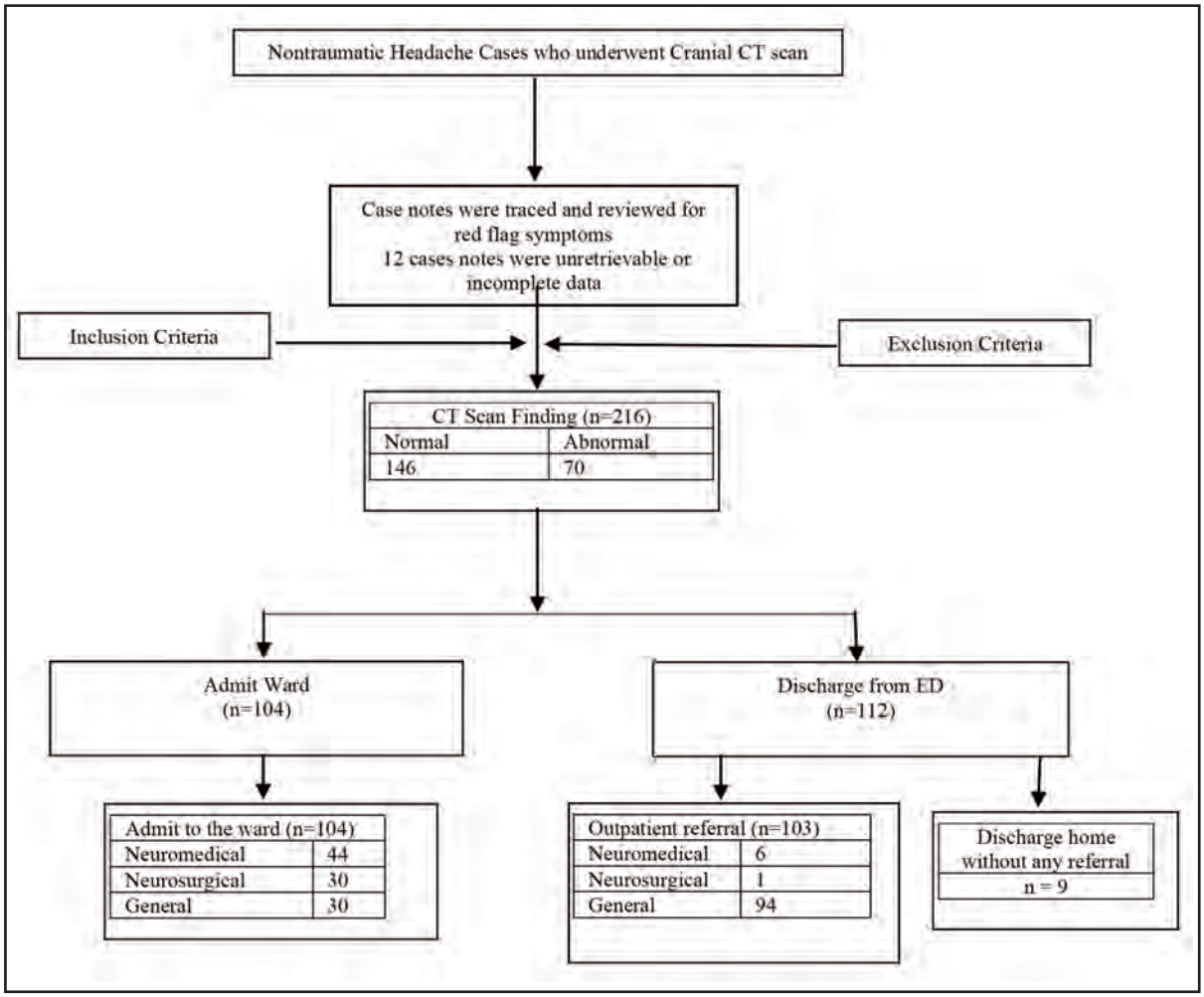

Fig. 1: The flow of the study and number of patients distribution

severe giddiness and persistent vomiting, which accounted for 40.3% and 36.6%, respectively. However, all the patients had more than one red flag symptom.

Table III shows three significant factors associated with abnormal CT scans among nontraumatic headache patients with red flag symptoms. The odds for abnormal CT scans for patients aged 50 years or older who had a new onset of headache were 3.21 times higher than those under 50 years old. The odds for abnormal CT scans for patients with SBP and MAP above 180mmHg and 120mmHg were 4.82 and 6.71 times higher than those with lower readings.

DISCUSSION

There was no sex difference in nontraumatic headache patients with red flag symptoms. This finding is similar to a previous study that found that 55.9% of the nontraumatic headache patients with red flags were female.[6] On the other hand, data have shown that most headache patients who present to the ED are female. The range is from 64 to 77.8%.[1,14] This is understandable, as the data covered all nontraumatic headaches, and some patients might not have any red flag symptoms. A community-based study in Malaysia also showed a higher prevalence of primary headaches, such as migraine and tension headache, in females than in males.[15]

Table III shows that a patient who was more than 50 years old and presented with a new onset of nontraumatic headache had a higher risk of abnormal CT scan findings. This finding is comparable with other studies that identified significant predictors based on age group for abnormal CT scans.[11,14,16] Another study found that patients who were older than 50 years old and complained of the worst headache could have serious underlying intracranial pathology.[17] Another study in Rostock, Germany, showed that the mean age for abnormal findings was 52 years old.[1] Multivariate analysis shows that age greater than 50 years old has an OR of 3.21 of having an abnormal cranial CT scan. Advancing age in headache patients (onset more than 65 years old) has also been shown to increase the risk of abnormal CT scans by 10-fold.[9]

Table III also shows a significant association of high SBP and MAP in a nontraumatic headache patient with at least one red flag symptom. An SBP of more than 180 mmHg and a MAP of more than 120 mmHg had ORs of 4.82 and 6.21,

respectively, for abnormal CT scan findings. The possible explanation for these findings is that there were 50 cerebral vascular accident (CVA) patients (41 patients had ischemic stroke and 9 patients had haemorrhagic stroke) who had abnormal CT scan findings. From a review, headache is a feature in CVA patients, presented in 16-65% of them, and more often involves posterior circulation stroke.[9]

With regard to the red flag symptoms, more than one-third of the patients had sudden onset of severe nontraumatic headache (thunderclap headache). This description of headache is known to be associated with spontaneous subarachnoid haemorrhage (SAH). However, a systematic review and meta-analysis found that only 7.5% of thunderclap headache patients had a final diagnosis of SAH.[18] However, it is unsure whether the history taking was properly done. A better clue for a thunderclap headache is a sudden onset headache, which peaks within 1 minute to 1 hour, is active during the onset and is accompanied by additional symptoms.[10] From this study, only 2 (2.6%) patients had SAH from 78 patients with thunderclap headache. This finding is much lower than that of a multi-centre cohort study in Canadian EDs.[19] An old study in Malaysia also estimated that the annual incidence of SAH in Malaysia was half that in Western countries, which was 3-4 per 100,000 population.[20]

Cranial CT scan findings showed that most of the patients had normal scans. Only 32.4% of the patients had abnormal cranial CT scan findings. Most of the abnormal findings were infarction, followed by tumours and intracranial bleeding. The lower percentage of abnormal cranial CT scans among red flag symptoms of headache patients is comparable with a previous study performed by Sobri et al., which found that 35.1% of the patients had abnormal CT scan findings.6 However, this result is much higher than that in a study from the ED in The Haque, where only 13.2% had abnormal CT scan findings.[11] In general, CT scans have a low yield, approximately 2% for abnormal CT scan findings for patients with a sole indication of headache.[21,22]

Unless we have more evidence, 'SSNOOP' can still be used as a risk stratification tool based on clinical criteria. Any misdiagnosis of secondary headache disorders has severe consequences, leading to disability or even mortality. With the added clinical criteria in SSNOOP10, we hope for better detection and care for headache patients with red flag symptoms, thus avoiding diagnostic pitfalls. However, this may also lead to low specificity and a higher percentage of negative CT scans. Additional criteria based on biomarkers have been investigated, such as copeptin for SAH. Nevertheless, the data are too limited to be included as part of a clinical recommendation.[23]

LIMITATIONS

As a retrospective study, some medical records were unretrievable or had incomplete data. In the majority of the cases, the description or nature of the headache, such as the site, character, radiation, exacerbation factors, relieving factors, and association with other symptoms, were inadequate. In addition, some cases had poor documentation on funduscopic and neurological examinations. However, these limitations are not unknown in the retrospective nature of a study. Somehow, selection bias was unlikely since the individual medical records were collected over a long period. Since there was also no cause-effect relationship, the study design was considered appropriate. A prospective study is required to determine the full spectrum of clinical characteristics in nontraumatic headaches with abnormal CT scans, including each feature from the SSNOOP. Another limitation is that the study was limited to a single tertiary ED in Malaysia.

CONCLUSION

The prevalence of abnormal CT scan findings in nontraumatic headache patients with red flag symptoms is 32%. Primary headache syndrome is the most common diagnosis, and CVA is the most common disease associated with abnormal scans. An age greater than 50 years old during the onset of headache, SBP greater than 180mmHg and MAP greater than 120mmHg have 3.21 times, 4.82 times, and 6.21 times higher risks of abnormal cranial CT scans among nontraumatic headache patients with red flag symptoms.

ACKNOWLEDGEMENT

The authors would like to thank all the staff in the ED and Record Unit for helping us during the data collection.

AUTHORS' CONTRIBUTION

The conception and design of the work and data acquisition by FAMN and KAB. Analysis and interpretation of data by FAMN, MMM, NY, and ASS. Manuscript writing by FAMN, KAB, and NY. All authors edited and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

None to declare

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Full blood count values in adolescents and its comparison by gender and ethnicity in Seremban district, Malaysia

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ABSTRACT

Background: Adolescence is when an individual undergoes development and growth. Many studies suggest variations in the number and size of blood cells during this period in various individuals. The full blood count (FBC) is often the starting point of medical investigations, which help diagnose a wide range of illnesses, infections, and diseases. This study aimed to report the mean FBC values and compare them by gender and ethnicity, using blood results from the thalassemia screening programme in Seremban District, Malaysia.

Materials and Methods: This cross-sectional study used secondary data from the thalassemia screening programme on Form 4 students aged 15-16 years from January 2018 to October 2018 by the Seremban District Health Office, Malaysia. These students participated in the thalassemia screening programme in which their blood samples were taken for FBC analysis. The data were extracted for this study.

Results: There were statistically significant gender-based differences for total white blood cell (WBC) count, neutrophils, lymphocytes, mixed WBC, and platelets. It was also observed that ethnic-specific differences were statistically significant for RBC count, platelets, platelet distribution width and mean platelet volume.

Conclusion: This study was able to report the mean FBC values among Malaysian adolescents with respect to their gender and ethnicity, of which there is a lack of published data.

KEYWORDS:
RBC indices, full blood count, Adolescent

INTRODUCTION

Adolescence is a period in which an individual undergoes development and growth. Many studies suggest variations in the number and size of blood cells during this period in various individuals.[1-3] These differences are attributed to accelerated growth due to hormonal and body changes during puberty, such as increasing haemoglobin levels.[1]

A few studies have been conducted in Malaysia to derive the normal reference values in adults.[4,5] For example, Ambayya et al.,[4] reported differences in ethnic and gender-specific full blood count (FBC) values in the Malaysian population. They included adolescents as part of their data. However, the data were not stratified for this age group. Hence, the normal values for this age group were not published. It would be clinically beneficial to distinguish the range of values for common laboratory investigations to help diagnose disease more precisely, with regard to age, gender, ethnicity, genetic differences, and environmental factors.[6]

FBC consists of red blood cell (RBC) indices, which include RBC count, haemoglobin (Hb), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), red cell distribution width (RDW); and white blood cells (WBC), and platelet indices such as platelet count, platelet distribution width (PDW), and mean platelet volume (MPV). MCV measures the average size of red blood cells, and MCH and MCHC measure the amount and percentage of Hb within the RBC. RDW measures the variation in size of RBC. Similarly, PDW measures platelet size variability and MPV, the average size of platelets.

This study aimed to determine the range of FBC values and compare them by gender and ethnicity based on the thalassemia screening programme results in Seremban District, Malaysia.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted using secondary data (FBC results) from the Thalassemia Screening Programme of Form 4 students in the Seremban District, which is situated to the south of Kuala Lumpur, the capital city. Between January and October 2018, these students participated in the screening programme, and their blood samples were drawn for FBC by School Health Teams under Seremban District Health Office. Blood samples were analysed by automated FBC analysers in the health clinic laboratories. The HydroDynamic focusing (DC detection) method was used for RBC indices and platelet count. At the

This article was accepted: 13 May 2022
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Table I: Comparison of haematological parameters and RBC indices between male and female adolescents from Seremban. (n=1534)

FBC Indices	Mean (SD)			Mean difference (95% CI)	t-stat (df)	p-value[a]
	Combined (n=1534)	Male (n=771)	Female (n=763)			
RBC count (million/m^3)	5.16 (0.55)	5.47 (0.48)	4.85 (0.43)	0.62 (0.57, 0.67)	26.46 (1516)	<0.001
Hb (gm/dL)	14.05 (1.42)	15.02 (1.11)	13.06 (0.94)	1.96 (1.86, 2.06)	37.13 (1500)	<0.001
Hct (%)	42.53 (3.92)	45.12 (2.89)	39.89 (2.95)	5.22 (4.93, 5.52)	35.03 (1531)	<0.001
MCV (fL)	83.25 (20.00)	82.85 (6.09)	83.66 (27.69)	-0.81 (-2.81, 1.20)	-0.79 (1532)	0.430
MCH (pg/dL)	27.41 (2.55)	27.64 (2.51)	27.17 (2.57)	0.47 (0.21, 0.72)	3.60 (1532)	<0.001
MCHC (g/dL)	33.00 (1.52)	33.31 (1.35)	32.70 (1.62)	0.61 (0.46, 0.76)	8.03 (1531)	<0.001
Total WBC count (mm^3)	8.23 (1.98)	7.85 (1.86)	8.61 (2.01)	-0.77 (-0.96, -0,57)	-7.75 (1531)	<0.001
Neutrophils (%)	53.67 (10.30)	51.63 (10.09)	55.83 (10.08)	-4.20 (-5.24, -3.17)	-7.99 (1468)	<0.001
Lymphocyte (%)	38.70 (106.70)	36.99 (8.38)	34.02 (7.41)	2.98 (2.17, 3.79)	7.25 (1469)	<0.001
Mixed (%)	10.61 (15.55)	10.79 (3.69)	9.58 (4.13)	1.21 (0.81, 1.61)	5.94 (1469)	<0.001
RDW_CV	13.53 (1.64)	13.42 (1.70)	13.64 (1.57)	-0.06 (-0.38, 0.05)	-2.55 (1524)	0.011
Platelet (mm^3)	314.49 (75.68)	302.33 (70.01)	326.79 (79.19)	-24.46 (-31.95, -16.97)	-6.40 (1504)	<0.001
PDW (%)	12.34 (1.91)	12.37 (1.83)	12.31 (2.00)	0.06 (-0.17, 0.29)	0.49 (1057)	0.622
MPV (%)	9.99 (0.99)	9.97 (0.94)	10.05 (1.04)	-0.03 (-0.15, 0.08)	-0.54 (1106)	0.593

[a] Independent t-test

Table II: Comparison of mean haematological parameters and RBC indices among ethnicity (n=1534)

FBC Indices	Mean (SD)			F-stat (df)	p-value[a]
	Malay (n=1228)	Chinese (n=138)	Indian (n=161)		
RBC count (million/m^3)	5.14 (0.52)	5.31 (0.78)	5.16 (0.55)	5.91 (2)	0.003
Hb (gm/dL)	14.04 (1.40)	14.14 (1.45)	14.02 (1.59)	0.36 (2)	0.698
Hct (%)	42.47 (3.88)	42.92 (3.86)	42.59 (4.27)	0.82 (2)	0.443
MCV (fL)	83.61 (21.92)	81.21 (11.00)	82.38 (6.20)	1.06 (2)	0.345
MCH (pg/dL)	27.45 (2.37)	27.11 (4.03)	27.32 (2.25)	1.26 (2)	0.283
MCHC (g/dL)	33.01 (1.54)	32.95 (1.61)	33.00 (1.36)	0.07 (2)	0.931
Total WBC count (mm^3)	8.26 (2.02)	7.95 (1.74)	8.19 (1.83)	1.62 (2)	0.198
Neutrophils (%)	53.64 (10.48)	55.40 (9.63)	52.49 (9.35)	2.82 (2)	0.060
Lymphocyte (%)	35.48 (7.99)	34.77 (8.50)	36.66 (8.15)	2.08 (2)	0.126
Mixed (%)	10.16 (3.95)	9.91 (3.15)	10.78 (4.59)	2.01 (2)	0.134
RDW_CV	13.51 (1.64)	13.68 (2.06)	13.50 (1.14)	0.68 (2)	0.509
Platelet (mm^3)	317.29 (76.95)	313.79 (76.87)	294.74 (61.97)	6.32 (2)	0.002
PDW (%)	12.22 (1.84)	12.37 (1.95)	13.08 (2.13)	11.06 (2)	<0.001
MPV (%)	9.91 (0.98)	10.14 (0.89)	10.38 (1.05)	14.56 (2)	<0.001

[a]One-way ANOVA

same time, the fluorescence flow cytometry method was utilised for WBC counts.

Sample Size Calculation

For sample size calculation, Openepi sample size calculator was used. The haemoglobin of <12 in males was 9%7 and in females was 14%, two-sided 95% Confidence Intervals (95%CI), power 80% and sample size calculated was 1342. An additional 20% (n=268) was added to compensate for missing data. Thus, the total required sample size of 1610 was determined.

Participants

Data for the study were sourced from the FBC results of 15-16 years old Form 4 secondary schools' students who participated in the National Thalassemia Screening Program. This programme commenced in Malaysia in 2016. In the Seremban district, there were a total of 54 secondary schools. In 2018, a total of 7903 students from these 54 schools had their FBC taken for screening by 14 school health teams (SHTs). Based on this screening, SHTs were able to identify cases with low haemoglobin levels and follow them up either for anaemia or proceed with further thalassemia investigation (haemoglobin analysis or DNA analysis).

Sample size calculated for this study was 1610. Estimating that at least 200 records could be retrieved from each SHTs, 9 SHTs were randomly selected (expecting at least 1800 samples). Unfortunately, only 1352 samples were retrieved. To complete the sample size, an additional two SHTs were selected using simple random sampling from the remaining five SHTs. This gave an additional 258 samples to complete the required 1610, from a total of 11 participating SHTs (Figure 1). Demographic data such as gender and ethnicity, as well as FBC parameters such as RBC indices, WBC, and platelet indices, were collected.

Inclusion and exclusion criteria

The inclusion criteria were Form 4 students from government secondary schools who participated in the thalassemia screening program in 2018. Non-Malaysian citizens were excluded from the sample.

Furthermore, students with anaemia were excluded. A Hb level of <11g/dL for females and <12g/dL for males4 were taken as the cutoff point for anaemia. Based on these criteria, 76 students (2 males and 74 females) were excluded from 1610, and the final data of 1534 students were analysed for this study.

Table III: Comparison of the obtained mean haematological values of adolescents in various populations

Parameter	Gender	Current study (n=1534)	Malaysian study[10] (n=199)	Ethiopian study[11] (n=249)	Japanese study[12] (n=12023)	Spain study[13] (n=581)	Kenya study[14] (n=298)	Saudi study[2] (n=1526)	Brazil study[15] (n=362)
RBC	Male	5.4	5.1	5.2	5.1	5.1	4.9	5.1	
(million/mm^3)	Female	4.8	4.7	4.9	4.6	4.4	4.7	4.9	
HGB	Male	15.0	13.9	14.8	15.2	14.8	13.1	14.2	
(gm/dL)	Female	13.0	12.4	14	13.3	13.3	12.2	13.8	
HT	Male	45.1		44.8	45.6	43.2	38.8	41.8	
(%)	Female	39.8		43.3	40.9	39.1	35.6	39.4	
MCV	Male	82.8	80.6	86.7		86.5	79	81.0	
(fL)	Female	83.6	81.4	88		87.5	78	81.0	
MCH	Male	27.6	27.6			29.6		27.8	
(pg/cell)	Female	27.1	26.7			29.9		27.1	
MCHC	Male	33.3	34.2	32.5		34.2		34.0	
(g/dL)	Female	32.7	33.9	32.2		34.1		33.6	
RDW	Male	13.4		14.1		13.2			
(%)	Female	13.6		13.7		13.1			
Total WBC count (mm^3)	Male	7.8		5.4		6.8	5.6	7.9	5.6
	Female	8.6		5.9		6.5	5.2	7.1	6.4
Neutrophils (%)	Male	51.6		45.5		52.0	33.9		55.3
	Female	55.8		50.6		55.2	38.4		60.9
Lymphocytes %	Male	36.9		40.0		36.7	39.3		35.7
	Female	34.0		38.9		36.9	42.3		29.6
Mixed	Male	10.7		14.5		8.8	16.8		
(%))	Female	9.5		10.5		7.6	16.1		
Platelets	Male	302.3		261	253	258	224		239
(mm^3)	Female	326.7		288	265	261	233		258

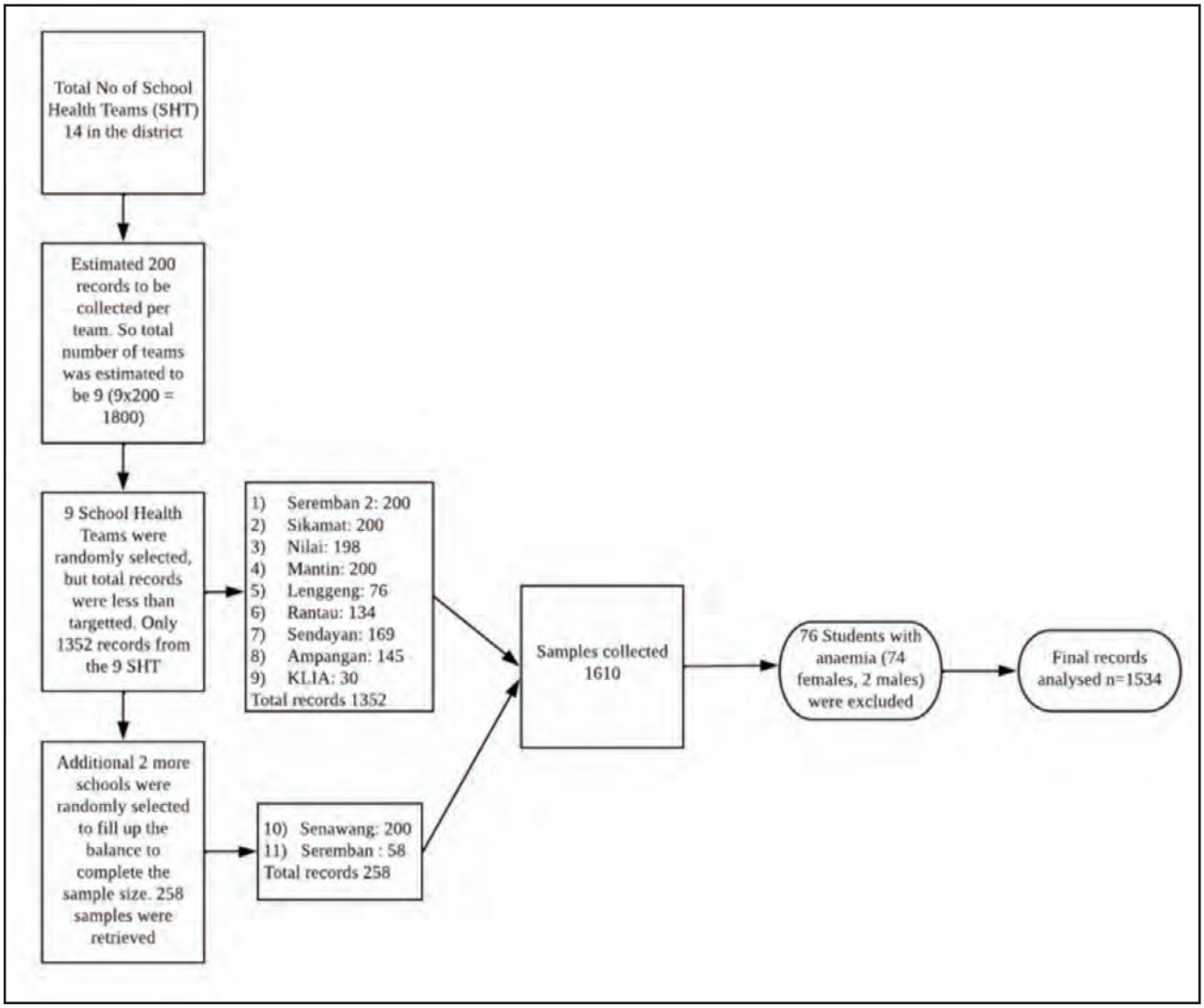

Fig. 1: Two stage sampling for record retrieval

Statistical Analysis

Data were anonymised and entered in Microsoft Excel for cleaning before importing into the Statistical Package for Social Sciences (SPSS) version 23.0 for analysis. Univariate analysis, namely independent t-test and one-way ANOVA was conducted in this study. The independent t-test was used to compare FBC indices between male and female adolescents. The level of significance was set at $p<0.05$. A one-way ANOVA analysis was further performed for comparison across the three ethnic groups (Malay, Chinese, and Indian). Post hoc test Dunnett-C was performed if Levene's test <0.05 and post hoc test Bonferroni was performed if Levene's test >0.05. A p value of <0.05 was considered statistically significant.

RESULTS

After excluding subjects with anaemia, a total of 1534 results were analysed for FBC values. There were 771 (50.3%) males and 763 (49.7%) females. By location, there were 1145 (74.6%) students in the urban areas compared to 389 (25.4%) in a rural setting. Malay ethnicity was the majority with 1228 (80.1%), followed by Indians 161 (10.5%), and Chinese 138 (9.0%). The mean FBC values for all parameters with the exception for MCV, PDW, and MPV showed a statistically significant difference between males and females (Table I).

FBC indices between the three ethnic groups (Malay, Chinese, and Indian) showed four variables to have a significant mean difference between groups for RBC, platelet, PDW, and MPV. Post hoc test Dunnett-C was performed for RBC and platelet (Levene's test <0.05) and post hoc test Bonferroni was performed for PDW and MPV (Levene's test >0.05) (Table II). Results of post hoc tests revealed that for RBC, there was a significant difference between Malay and Chinese [mean diff (95% CI): -0.17 (-0.33, -0.01) p=0.003]. Platelet mean differed significantly between the Malay and Indian groups [mean diff (95% CI): 22.54 (9.86, 35.23) p=0.002]. Mean of PDW differed significantly between Malay and Indian [mean diff (95% CI): -0.86 (-1.29, -0.42) p≤0.001] as well as Indian and Chinese [mean diff (95%CI): 0.71 (0.10, 1,32) p=0.017]. MPV

between Malay and Indian differed [mean diff (95% CI): -0.47 (-0.69, -0.25) p≤0.001].

DISCUSSION

Summary of the Main Findings

The current study observed statistically significant gender-based differences amongst the study population of 15-16 years old adolescents for RBC indices such as RBC count, Hb, HCT, MCH, MCHC, and RDW. In addition, for haematological parameters, the present study also found statistically significant gender-based differences for total WBC count, neutrophils, lymphocytes, mixed WBC, and platelets. However, ethnic-specific differences were statistically significant only for RBC count, platelets, PDW, and MPV.

Findings in Comparison to Previous Studies

Britannica encyclopedia defines adolescence as the intermediary phase of physical and psychological changes between childhood and adulthood.[8] On the other hand, the World Health Organization (WHO) age group defined adolescents as anyone between the ages 10 and 19.[9]

There is a lack of published haematological parameters reference data in adolescents in Malaysia. The present study will discuss the most significant gender-based differences compared to other studies. Our findings show statistically significant differences between males and females for FBC parameters. The differences were observed for the mean values of RBC count, Hb, HCT, MCH, MCHC, RDW, total WBC count, neutrophils, lymphocytes, mixed WBC, platelets, PDW, and MPV (Table I). These findings are consistent with the study by Menard,[10] who reported gender-based differences. The gender-based differences have been reported in various countries. The factors contributing to these differences could be menstruation, hormonal influences of androgen, estrogens, and testosterone on erythropoiesis, and the relatively high prevalence of iron deficiency anaemia in women.[10]

A few studies on mean RBC indices across several studies conducted in Malaysia, Ethiopia, Japan, Spain, Kenya, and Saudi Arabia are compared with current study results in Table 3. However, the causes of these differences still need to be studied in detail. The highest values for RBC count for adolescents were reported in both males and females. However, in the current study, the RBC values in males were higher compared with other studies (Table III). There is a lack of accurate correlation between these differences in various populations. However, on average, RBC count is seen lower in females than males, attributed to the effects of oestrogen and androgens on erythropoiesis.[11]

Regarding RBC indices, Foo et al.,[7] in their study involving adolescents aged 12-19 years (94 males and 105 females), reported the median reference intervals (RI) of Hb, HCT, and MCV values for a healthy adolescent population from Sabah, Malaysia.[7] In our study, the values for MCH in males were in agreement; however, Hb and MCV values for males and females showed higher mean values, and MCHC (both genders) were lower than those reported for adolescents in Sabah, Malaysia. In the study from Spain,[12] the MCV, MCH, and MCHC values reported are higher than in the current study (Table III).

Furthermore, our study reports higher MCV values in Malaysian male and female adolescents than those reported by El-Hazmi and Warsy.[2] They studied 1526 children aged 13–15 years from the Central Province of Saudi Arabia. These differences could be explained by covariates that can influence the values, such as nutritional status or using different laboratory methods in these populations.

In this study, females showed significantly lower RBC count, Hb, and HCT values compared to males (Table I). This is contrary to findings by Foo et al.[7] and El-Hazmi and Warsy,[2] in which no significant differences in RBC count were noted between males and females. This outcome could be due to nutritional status, menarche age, or may be due to ethnic differences between Malaysian and Saudi adolescent populations. This issue needs to be further explored. Nevertheless, the current findings concur with those reported from the National Health and Nutrition Examination Survey (NHANES) study on adolescents from the USA and data from Spain[12], revealing that males show significantly higher RBC indices than females. These differences could be due to the influence of the endocrine disruption during puberty, hormone androgen on erythropoiesis, and menstrual losses.[13]

The values of total WBC count for males and females showed statistically significant variation. The current study observed significant differences in WBC differentials percentages between males and females. However, there is minimal literature on WBC value ranges for adolescents. Regarding WBC count, the current study showed higher mean values for males and females than those reported for Ethiopia, Kenya, and Brazil[14–16] adolescents. However, in Saudi Arabia,[2] the WBC values reported in males are higher than in the current study (Table III). These findings are supported by previous studies implying that haematological values are affected by several factors such as ethnic background and incidence of infections and parasitosis.[1,17]

Moreover, there was a statistically significant difference in platelet count between the two sexes in this study. The platelet count reported in Japanese, Kenya, Spain, and Brazil studies in adolescents is lower than in the present study.[12,15,16,18] The present study observed higher platelet counts in females than in other studies (Table III). A few studies have demonstrated gender-dependent differences in platelet count.[19,20] In women, the platelet count is higher than in men, reflecting different hormonal profiles or a compensatory mechanism associated with menstrual blood loss.[20]

Higher WBC and platelet count were observed in the present study compared to other population ranges for adolescence. The exact cause is unknown; however, the influence of environmental, genetic factors or undetected subclinical illness cannot be ruled out. Gender-based differences in the total WBC, neutrophil, and platelet counts have been reported in all ethnic groups and could be related to biological differences.[19] For ethnic groups, reference values for common haematological investigations are usually not

established separately. However, various studies have shown that racial/ethnic differences in reference values of various laboratory tests were mainly between blacks and whites[19,21] Whites show significantly higher values than blacks for total WBC, neutrophil counts,[22] platelet counts,[19] HCT, MCHC, MCH, and Hb,[22] and significantly lower mononuclear and lymphocyte percentages. In the current study, the RBC count, platelet count, PDW, and MPV showed a statistically significant difference between the Malays, Chinese, and Indians (Table II). These differences could be associated with genetic variations in these ethnicities.

Malaysia has a multiracial population. A study from Malaysia[4] compared haematological intervals in multiethnic adult subjects; however, they concluded that there were no ethnic-specific differences. Haniff et al.,[22] from their multicentre analysis of pregnant females, found that the average Hb level of the Malays was significantly lower than the Chinese. However, in the current study, the RBC indices showed no statistically significant ethnic difference for Hb, MCV, MCH, and MCHC values (Table II).

The RBC count was significantly higher in Chinese than in Malays and Indians. However, the magnitude of the differences was small. The high RBC count in Chinese could be due to obesity, lifestyle behaviour, or a sign of underlying illness; however, it does not always show a medical condition.[24] We did not record the BMI of subjects in this study; therefore, the correlation of high RBC count with BMI is lacking in this study. We also observed a significantly lower platelet count in Indians compared to Malays. The exact reason for low platelet count is not well studied, but the influence of genetic, dietary, and environmental factors can be speculated as reported in other studies.[25,26] Researchers from India in 2014 reported regional differences in platelet count and observed low platelet count in Chennai compared to other regions of India.[27] Indians in Malaysia have ancestors who migrated mainly from regions in South India,[28] such as Chennai. This genetic influence may account for the lower platelet count. Nevertheless, this study proposes that all these ethnicity-based differences are not clinically significant as the values are still within the normal range for RBC and platelet count.

The comparative published data on racially based differences in platelet count is sparse. The differences in mean platelet count related to ethnicity, gender, and age are not clearly explained by variables known to impact platelet count. Instead, these differences could be explained by genetic influences on the platelet count.[23] Compared with Caucasian ranges, lower platelet counts have been confirmed for Africans and Afro-Caribbean women.[18,24] These differences are sufficient to be of practical importance in interpreting counts around the lower end of the reference range. In this study, platelet count was higher in Malays than in Chinese and Indians. Mean platelet count showed statistically significant differences among ethnicities. Malays showed lower MPV than the other two ethnicities (Table III).

Strengths and Limitations

This study is one of the few studies for this age group reporting the laboratory values for haematological parameters and RBC indices in adolescents in Malaysia. It remains the key strength of this study. Ambayya e al4 included this age group as part of their data; however, data were not stratified for this age group. Therefore, the normal or expected values for this age group were not known. These findings of the normal haematological values could contribute to the body of knowledge and help physicians provide greater precision in diagnosis to offer the right intervention and treatment of related diseases in adolescents.

Another limitation was that this study was confined only to the three major ethnic groups (Malay, Chinese, and Indian) and did not include the other ethnicities in the country. The data captured FBC values for adolescents aged 15-16 years old and not the entire adolescent population age group.

CONCLUSION

There were statistically significant gender-based differences for total WBC count, neutrophils, lymphocytes, mixed WBC, and platelets. Gender, independently or interactively, can determine differentials in disease burden, and their blood parameter values may influence early diagnoses and interventions. It was also observed that ethnic-specific differences were statistically significant for RBC count, platelets, PDW, and MPV. This study could be an impetus for further follow-through studies to develop a home-based Malaysian Reference Interval standard that can be used nationwide.

FUNDING

This research was funded by the International Medical University grant number IMU 470/2020.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki as revised in 2013. Also, ethical approval was obtained from Medical Research & Ethics Committee (MREC # KKM/NIHSEC/ P20-2406 (4) dated 01-Dec-2020). All information collected was strictly confidential, and anonymity was ensured.

INFORMED CONSENT STATEMENT

Permission was obtained from Seremban District Health Office to use this secondary data. However, individual consent from parents was not taken as this data was collected in 2018. However, steps have been taken to anonymise the data for this study.

ACKNOWLEDGEMENTS

The authors would like to thank the Director-General of Health Malaysia for the permission to publish this article. The authors are also thankful to the State Health Director Negeri Sembilan for their collaboration in the planning, executing, and supporting of the research study database.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Risk factors for complications and survival outcomes of *Klebsiella pneumoniae* Bacteraemia in Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia

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ABSTRACT

Introduction: Mortality of *Klebsiella pneumoniae* (*K. pneumoniae*) bacteraemia was reported to be on the rise globally. The 30-day mortality rate of *K. pneumoniae* bacteraemia ranges from 16% to 55% in Beijing, Shanghai, and Taiwan. However, there is a lack of research on the survival outcomes of *K. pneumoniae* bacteraemia in Malaysia. The objectives of this study were to determine the poor prognostic factors and predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

Methods: This was a retrospective cohort study of patients with *K. pneumoniae* bacteraemia in Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM). We included adult patients with blood cultures positive for *K. pneumoniae* between 1 January 2016 and 31 December 2019. Those with polymicrobial bacteraemia were excluded. Medical records were reviewed to obtain the socio-demographic data, gender, underlying comorbidities, invasive procedures at presentation, sources of bacteraemia, and whether appropriate empirical and definitive antibiotics was given on time. Data regarding complications of *K. pneumoniae* bacteraemia, including liver abscess, endopthalmitis, septic shock, Quick Pitt (qPitt) bacteraemia score defined as hypothermia, hypotension, respiratory failure, cardiac arrest, and altered mental status and stay in intensive care unit (ICU) were also recorded. The main outcome measure used was the survival in 14 days. Summary of statistical analysis was done.

Results: A total of 260 patients with *K. pneumoniae* bacteraemia were included. All patients received appropriate empirical and definitive antibiotics within 24 h of the time that the sample for index blood cultures was obtained. Respiratory infection, septic shock, qPitt bacteraemia score ≥2, solid organ malignancy, stay in ICU, central venous line insertion at presentation, urinary catheterisation at presentation, and in-patient mechanical ventilation were identified as independent predictors of mortality in *K. pneumoniae* bacteraemia. The rate of complications such as liver abscess, endophthalmitis, ICU admission, and septic shock was not significantly different between survivors and non-survivors. The 14-day in-hospital mortality rate was 12.3%. The median length of hospitalisation was 11 days (IQR 6 - 19) . The predictors of poor prognosis for 14 days in-hospital mortality for *K. pneumoniae* bacteraemia were as follows: qPitt bacteraemia score ≥2, central venous line insertion, indwelling urinary catheter at presentation, and in-patient mechanical ventilation. Timing from *K. pneumoniae* bacteraemia event to death among those qPitt bacteraemia scores ≥2 was only for 9 days or less.

Conclusions: The 14-day in-hospital mortality of patients with *K. pneumoniae* bacteraemia in our setting was low. The qPitt bacteraemia score ≥2 was the strongest predictor of poor prognosis for 14-day in-hospital mortality in patients with *K. pneumoniae* bacteraemia. The qPitt bacteraemia score should be proposed to be used as a bedside screening tool for gram negative bacteraemia in our daily clinical practice, which is also useful for predicting mortality in critically ill patients.

KEYWORDS:
risk factors, hospital mortality, Klebsiella pneumoniae bacteraemia

INTRODUCTION

Gram-negative bacteraemia is a common cause of morbidity and mortality worldwide. *K. pneumoniae* was the second commonest gram-negative pathogen after *Escherichia coli*.[1] In the United States, *K. pneumoniae* causes hospital-acquired urinary tract infection, septicaemia, pneumonia, and soft tissue infection.[2] This was of great concern due to increasing antimicrobial resistance globally seen with *K. pneumoniae*. Mortality of *K. pneumoniae* bacteraemia has increased due to multifactorial reasons such as underlying comorbidities, inappropriate empirical antibiotics treatment, and invasive procedures prior to bacteraemia.[3] Delay in initiation of effective antibiotics therapy for more than 48 hours after diagnosis of *K. pneumoniae* bacteraemia was associated with more than 1.5- to 2-fold increase in morbidity and mortality risk.[4]

This article was accepted: 18 May 2022
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Several studies that focused on *K. pneumoniae* bacteraemia found a high mortality rate in China and Europe.[5,6] However, similar large research in our geographical area was still missing. Most reports analysed the molecular epidemiological aspects of hypervirulent *K. pneumoniae*, or focused on the special group such as Extended Spectrum Beta-Lactamase (ESBL) K. pneumoniae of the isolates.[7-9] Less attention has been focused on the predictors of mortality caused by K. pneumoniae. The objectives of this study were to determine the poor prognostic factors and predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

MATERIALS AND METHODS

A retrospective, cohort study was conducted at Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM), which is a 1084-bed teaching hospital located in an urban setting. The study period was from 1 January 2016 to 31 December 2019. All patient aged over 13 years, who developed monomicrobial blood culture positive for *K. pneumoniae* during the study period were included. Relevant data were retrieved from patients' medical records and electronic microbiologic database. Patient demographics, gender, underlying comorbidities, invasive procedures at presentation, and sources of bacteraemia were collected. The severity of illness was calculated by qPitt bacteraemia score. The main outcome measure used was the 14-day in-hospital mortality rate.

K. pneumoniae bacteraemia was defined as an infection confirmed by blood culture positive for *K. pneumoniae*. Patients with further positive blood cultures taken within 14 days from the first specimen and positive for the same organism were considered the same episode of bacteraemia. However, it was considered as a non-related, independent episode, if more than one episode occurred within more than a 2-week interval in the same patient who had been properly treated and clinically cured. Bacteraemia was classified as primary when the patient had a positive *K. pneumoniae* cultured from one or more blood cultures, and the organism cultured from blood was not related to an infection at another site.[10] Bacteraemia was considered secondary when the patient had a positive *K. pneumoniae* cultured from one or more blood cultures and the organism cultured from blood was related to an infection at another site.[10]

Appropriateness of empirical therapy was defined as therapy (with at least one agent, if more than one agent was used), given within 24h of time that the sample for index culture was obtained, to which the isolate was found to be susceptible on the final antimicrobial susceptibility report and the doses used were appropriate for the end organs function of the patients.[11] Appropriate definitive antimicrobial therapy was defined as therapy given after antimicrobial susceptibility was reported, which ranged from 2-4 days from onset of bacteraemia, and the treatment administered was susceptible to the *K. pneumoniae* strain.[11] Liver abscess was defined by the coexistence of blood culture positive for *K. pneumoniae* and evidence of an intrahepatic abscess cavity by ultrasonography or computed tomography.[12] Endophthalmitis was defined as decreased visual acuity, pain, hypopyon, or severe anterior uveitis in a patient with concurrent *K. pneumoniae* bacteraemia.[12]

Survivors were defined as those who survive beyond 14-day in-hospital setting. Non-survivors were defined as those who passed away within 14-day in-hospital. Septic shock was defined as sepsis associated with evidence of organ hypoperfusion and either a systolic blood pressure of <90 or 30mmHg less than the baseline value or a requirement for the use of vasopressor to maintain blood pressure.[13] The severity of bacteraemia was calculated using the qPitt bacteraemia score, each of the following contributes to 1 point: evidence of hypothermia (temperature<36°c), hypotension (systolic BP<90mmHg or vasopressor use), respiratory failure (respiratory rate ≥25 breaths per min or need for mechanical ventilation), cardiac arrest, and altered mental status.[12] A qPitt bacteraemia score ≥2 was associated with higher mortality risks.[12]

Community-acquired infection was defined as a gram-negative bacteraemia detected within 48 hours of hospital admission, and the patient had not received healthcare in either the community or hospital in the previous 28 days.[14] Hospital-acquired infection was defined as infection that occurred more than 48 hours after hospital admission.[14]

Data analysis was carried out on Statistical Package for Social Science (SPSS) software version 23. At 95% confidence interval (95%CI), $p<0.05$ was considered to be significant. Categorical variables were expressed as frequency and percentage (%), and general associations between categorical variables were examined using Chi-square test. Finally, Kaplan–Meier analysis was used to estimate the survival function (hazard ratio, HR) of *K. pneumoniae* bacteraemia at a respective time interval. Hazard ratio is defined as the hazard rate comparing the rate of event in one group versus the other over time. Multivariate cox regression analysis was then used to determine predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

RESULTS

A total of 260 *K. pneumoniae* bacteraemia cases were extracted from our database. Out of 260 cases, there were 229 patients with 1 episode, 11 patients with 2 episodes, and 3 patients with 3 episodes of *K. pneumoniae* bacteraemia. All 260 cases were included in the study. There were a total of 139 males and 121 females in the study. The mean age of the patients who died was 68 while the mean age of those who survived was 64. There were a total of 131 Malay patients (50.4%), 101 Chinese patients (38.8%), 25 Indian patients (9.6%), and 3 foreigners (1.2%) in the study. There were a total of 46 patients with primary bacteraemia while there were 221 patients with a secondary source of bacteraemia (Table I).

There was no significant difference in survival outcomes between males and females. There was no significant difference in mortality among patients who had diabetes (p=0.073) or hypertension (p=0.421) compared to those without. Likewise, there were no significant differences between patients who survived or died for the following comorbidities ischaemic heart disease (p=0.631), end stage renal failure (p=0.481), liver cirrhosis (p=0.685), chronic lung disease (p=0.764), haematological disease (p=0.596), and immunodeficiency (p=0.097). Patients who had organ

Table I: Comparison of clinical characteristics and survival outcomes of K. pneumoniae bacteraemia

Characteristics	Total (n=260) n (%)	Death (n=32) n (%)	Alive (n=228) n (%)	p value
Demographic data				
Age, years (mean)		68 (SD 12)	64 (SD 15)	
Gender				
Male	139 (53.5)	19 (59.4)	120 (52.6)	0.474
Female	121 (46.5)	13 (40.6)	108 (47.4)	
Ethnicity				
Malay	131 (50.4)	15 (46.9)	116 (50.8)	
Chinese	101 (38.8)	12 (37.5)	89 (39)	0.454
Indian	25 (9.6)	4 (12.5)	21 (9.3)	
Foreigner	3 (1.2)	1 (3.1)	2 (0.9)	
Underlying disease				
Diabetic mellitus	144 (55.4)	13 (40.6)	131 (57.5)	0.073
Hypertension	163 (62.7)	18 (56.3)	145 (63.6)	0.421
Ischaemic heart disease	72 (27.7)	10 (31.3)	62 (27.2)	0.631
End stage renal failure	30 (11.5)	2 (6.3)	28 (12.3)	0.481
Liver cirrhosis	9 (3.5)	2 (6.3)	7 (3.1)	0.685
Chronic lung disease	6 (2.3)	0 (0.0)	6 (2.6)	0.764
Solid organ malignancy	45 (17.3)	12 (37.5)	33 (14.5)	0.001
Haematology malignancy	8 (3.1)	0 (0.0)	8 (3.5)	0.596
Immunodeficiency	24 (9.2)	6 (18.8)	18 (7.9)	0.097
Complications				
Liver abscess	29 (11.2)	1 (3.1)	28 (12.3)	0.123
Endophthalmitis	1 (0.4)	0 (0.0)	1 (0.4)	0.707
Septic shock	52 (20.0)	20 (62.5)	32 (14.0)	<0.001
QPitt bacteraemia score ≥2 high	40 (15.4)	27 (84.4)	13 (5.7)	<0.001
Stay in ICU	17 (6.5)	10 (31.3)	7 (3.1)	<0.001
Invasive procedures				
Central venous line	28 (10.8)	8 (25.0)	20 (8.8)	0.014
Urinary catheterisation	49 (18.8)	15 (46.9)	34 (14.9)	<0.001
Mechanical ventilation	13 (5.0)	10 (31.3)	3 (1.3)	<0.001
Surgical intervention	54 (20.8)	6 (18.8)	48 (21.1)	0.764
Source of bacteraemia				
Primary	46 (17.7)	9 (28.1)	37 (16.2)	0.099
Secondary				
Respiratory tract infection	64 (24.6)	16 (50.0)	48 (21.1)	<0.001
Urinary tract infection	53 (20.4)	3 (9.4)	50 (22.0)	0.099
Intra-abdominal infection	67 (25.8)	5 (15.6)	62 (27.2)	0.161
Skin infection	18 (6.9)	0 (0.0)	18 (7.9)	0.099
Catheter-related bloodstream infection	19 (7.3)	0 (0.0)	19 (8.3)	0.09
Antibiotics				
Amoxicillin–clavulanate	174 (66.9)			
Cefuroxime	49 (18.8)			
Piperacillin–tazobactam	22 (8.5)			
Ceftriaxone	15 (5.8)			
Time from admission to positive blood culture				
48hours or less, community-acquired infection	255 (98)	32 (100)	223 (98)	
more than 48 hours, hospital-acquired infection	5 (2)	0 (0.0)	5 (2)	
Duration of antibiotics use, days		14 (SD 19)	16 (SD 21)	
Time of first antibiotic administration	24 hours			

*QPitt: quick Pitt, ICU: intensive care unit

Table II: 14-day in-hospital mortality predictors of K. pneumoniae bacteraemia

	Crude			Adjusted		
	HR*	95% CI	p value	HR	95% CI	p value
Respiratory tract infection	3.38	1.49–7.66	0.004	1.63	0.60–4.41	0.334
Septic shock	7.78	3.30–18.35	<0.001	0.65	0.23–1.79	0.399
QPitt bacteraemia score ≥2	45.48	13.50–153.25	<0.001	37.5	10.78–130.38	<0.001
Solid organ malignancy	1.66	0.65–4.21	0.286	2.2	0.72–6.75	0.166
Stay in ICU	5.53	2.18–14.04	<0.001	3.55	0.60–21.00	0.163
Central venous line	1.67	0.57–4.90	0.354	5.62	1.18–26.76	0.03
Urinary catheterisation	4.84	2.13–10.99	<0.001	3.38	1.10–10.44	0.034
Mechanical ventilation	11.38	4.67–27.76	<0.001	5.98	1.26–28.29	0.024

*HR: Hazard ratio, defined as the hazard rate of event in one group versus the other over time

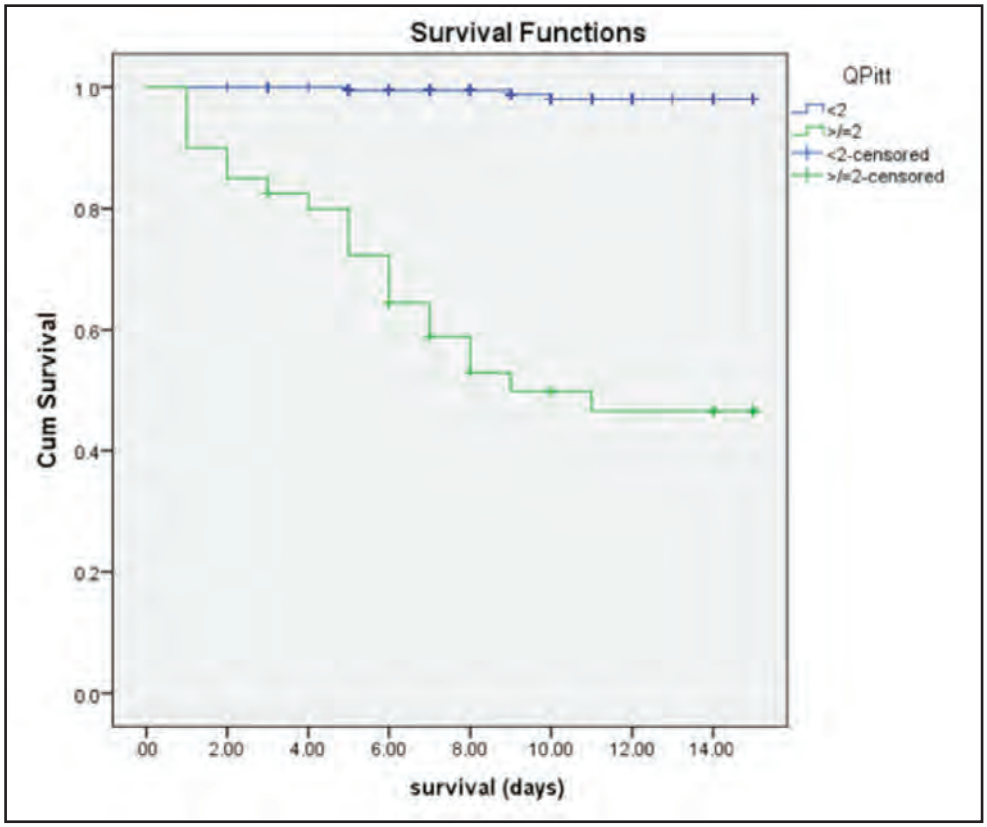

Fig. 1: Kaplan–Meier survival curve of *K. pneumoniae* bacteraemia in QPitt bacteraemia scores ≥2

QPitt bacteraemia scores	Median time effect (death, days)	95% CI	Log Rank test (df)	*p value*
<2	No event			
≥2	9	5.72–12.28	112.9	<0.001

malignancy were likelier to die than those who did not (p=0.001) (Table I).

K. pneumoniae bacteraemia was associated with the respiratory source of infection (p<0.001). Primary bacteraemia, urinary tract infection, intra-abdominal infection, skin infection, and catheter-related bloodstream infection did not show a significant difference in mortality. There were no significant differences in liver abscess and endophthalmitis between survivors and non-survivors, p=0.123 and p=0.707, respectively. Septic shock, ICU stay, and a raised qPitt bacteraemia score ≥2 were associated with significantly higher mortality rate, respectively (p<0.001). There were 52 patients had septic shock but only 17 (32%) patients were admitted to ICU. Furthermore, 61% (32/52) of patients with septic shock survived (Table 1).

Table I illustrated patients who had invasive procedures like CVL insertion (p=0.014), urinary catheter insertion (p<0.001), and mechanical ventilation (p<0.001) had significantly higher mortality rates. None of the cases received inappropriate empirical or definitive antibiotic therapy. The 14-day in-hospital mortality was 12.3% (32/260).

Amoxicillin–clavulanate was the most commonly used empirical agent (66.9%, 174/260) and 18.8% (49/260) of cases that received cefuroxime. Piperacillin–tazobactam was used in 8.5% (22/260) of patients. Ceftriaxone was administered to 5.8% (15/260). There were a total of 255 patients with community-acquired infection (98%) while there were 5 patients with hospital-acquired infection (2%). The median duration of antibiotics for those alive was 16 days while the median duration of antibiotic for those dead was 14 days. All patients received antibiotics within 24 hours on admission or blood culture being taken (Table I).

Figure 1 illustrated the median overall survival for patients with high qPitt bacteraemia score ≥2 is 9 days (95%CI: 5.72, 12.28).

Table II illustrates that the most significant predictors related to 14-day in-hospital mortality was qPitt bacteraemia score with Hazard Ratio, HR=37.50 (95%CI: 10.78, 130.38). This is followed by mechanical ventilation (HR 5.98, 95%CI: 1.26, 28.29), central venous line insertion (HR 5.62, 95%CI: 1.18, 26.76), and indwelling urinary catheter (HR 3.38, 95%CI: 1.10, 10.44).

DISCUSSION

This study shows a low mortality rate of 12.3% in HCTM compared to other regional centres that range from 16% to 55% in Beijing, Shanghai, and Taiwan.[3,15,16] The difference in mortality rates across the different studies is most likely due to the differences in the population studied. The mortality rate in Beijing was 16% which is closest to our study. The mortality rate in Shanghai was high at 25%, and this is most likely due to inappropriate use of empirical antibiotics in as high as 77% of patients. The mortality rate in Taiwan was 55%, and this reflects their study population with a higher mean age of 73 and almost 50% of patients have chronic lung disease.

The most common sources of infections in the present cohort were respiratory infection, intra-abdominal infection, and urinary tract infection, similar to previously identified sources of *K. pneumoniae* bacteraemia.[17] Intra-abdominal infections in our study comprised gastrointestinal sepsis, hepatobiliary sepsis, cholangitis, cholecystitis, peritonitis or spontaneous bacterial peritonitis, and intra-abdominal abscesses (excluding liver abscess). In view of this, imaging should be considered accordingly.

In this study, 61% of patients with septic shock survived in non-ICU setting. Only a small percentage of patient gained access to ICU. This was because all patients received timely and appropriate empirical and definite antibiotics like amoxicillin–clavulanate, ceftriaxone, and cefuroxime following the local national antimicrobial guideline, and this potentially contributed to the lower mortality rates. A large number of studies found that septic shock and ICU admission were independent risk factors for mortality in patients with *K. pneumoniae* bacteraemia, and inappropriate antibiotics led to increased mortality.[18,19] Thus, the administration of appropriate antibiotic treatment can improve patient survival outcomes.

Battle et al.,[12] derived the qPitt bacteraemia score and determined that a score of 2 or more carries higher mortality. Our study used the same cut-off value and arrived at the same conclusion that qPitt bacteraemia of two or more carries higher mortality.

The presence of indwelling urinary catheterisation, central venous line, and mechanical ventilation had been previously reported as a significant risk factor for *K. pneumoniae* bacteraemia.[2,3] The role of invasive devices has been implicated in colonisation and infection by destroying the continuum of the skin or mucosa.[3]

There were fewer cases of liver abscess and endophthalmitis found in this series when compared to studies from China, New York, and Taiwan.[3,7,15] It is still controversial whether all patients diagnosed with *K. pneumoniae* bacteraemia needed an ultrasound to rule out a liver abscess. The incidence of liver abscess in *K. pneumoniae* bacteraemia was as low as 2% to as high as 18% in countries like Taiwan.[20,21] The majority of cases were caused by ascending infection from a biliary tract pathology rather than primary bacteraemia.[21]

Future studies should look at the proportion of patients with *K. pneumoniae* who are being screened for endophthalmitis and liver abscess. These factors might have directly influenced the mortality outcome as seen in the Taiwan study that the presence of endopthalmitis and liver abscess did carry a devastating mortality.[7,22] The worst outcome of endogenous endophthalmitis was irreversible blindness if there was a delay in the diagnosis and antibiotic treatment.[23] Thus, patients with *K. pneumoniae* bacteraemia in HCTM should be considered to undergo ophthalmologic screening routinely.

The present study had several limitations. Clinical data were obtained retrospectively from medical records, and therefore, some differences in physician practices will affect the accuracy of information. Only cases of *K. pneumoniae* infection associated with positive blood culture were included in the study. Patients with significant infections which may have been bacteraemia but who did not have blood cultures were not included in the study. This was a single-centre study, including 260 cases with detailed clinical analysis, and further multi-centric, a prospective design to allow exploration of a number of important data. Researchers could look at the genotype strain analysis of K. pneumoniae which at the time of study was not available in HCTM.

This study is a first in Malaysia and is of paramount importance as it lays the groundwork for future studies.

CONCLUSION

The 14-day in-hospital mortality of patients with *K. pneumoniae* bacteraemia in our setting was low. The qPitt bacteraemia score ≥2 was the strongest predictor of poor prognosis for 14-day in-hospital mortality in patients with *K. pneumoniae* bacteraemia. The qPitt bacteraemia score should be proposed to be used as a bedside screening tool for gram-negative bacteraemia in our daily clinical practice, which is also useful for predicting mortality in critically ill patients.

AUTHOR CONTRIBUTIONS

(1) concept of design: ASH, PP, SAS, RR, NK, CLL, (2) Acquisition of data: ASH, PP, RR, (3) Analysis or interpretation of data: ASH, PP, SAS, (4) Drafting of article: ASH, PP, (5) Critical revision for important intellectual content: PP, SAS, RR, NK, CLL

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

CONFLICTS OF INTEREST

All authors have disclosed no conflicts of interest.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the staffs especially Prof Syahrul Sazliyana at Department of Medicine, Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia for their participation in this study.

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

ETHICS APPROVAL
This research was approved by the Health Research Ethical Committee of the University Kebangsaan Malaysia Teaching Hospital with the approval project code FF-2020-136. This is a study involving data collection through medical records, therefore informed consent from patients is not required.

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ORIGINAL ARTICLE

Prevalence and psychosocial impact of acne vulgaris among high school and university students in Sarawak, Malaysia

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ABSTRACT

Background: Acne vulgaris is a common skin condition that affects adolescents and young adults. Its psychosocial impact can be significant. The primary objective of this study was to determine the prevalence of acne vulgaris and its psychosocial impact among high school and university students in Kuching, Sarawak. In addition, the clinical characteristics of acne and its potential predisposing factors were assessed.

Methods: This cross-sectional study was conducted among high school and university students in Kuching, Sarawak. A team of dermatology-trained doctors examined a representative sample of high school and university students aged 16 to 25 years to identify acne vulgaris. The Dermatology Life Quality Index (DLQI) was used to assess the psychosocial impact of acne on affected individuals. The Global Acne Grading System (GAGS) was used to determine the severity of acne. Demographic data and clinical characteristics of acne were recorded.

Results: A total of 582 students aged 16 to 25 years were recruited. The overall prevalence of acne vulgaris was 75.8% (n=441). The prevalence of acne was highest (85.5%) in the age group of 16-18 years. There was a significantly higher tendency for male students to have moderate to severe acne (p=0.010). A significantly higher proportion of female students had impaired quality of life (p<0.001) compared to male students. In comparison to male students, the mean DLQI scores were significantly higher in female students in the domains of 'Work and school' and 'Personal relationship' (p<0.05). There were 41 students who had a very large impact on the quality of life with a DLQI score of 11-20 and 34 (82.9%) of them had mild acne. There was a significantly higher proportion of students who had frequent insomnia in the group of students with acne compared to those without acne (11.6% vs. 4.3%, p=0.011). There was no significant association of acne vulgaris with dietary intakes, such as chocolates, sweets, potato chips, yoghurt, milk, fried chicken, ice cream, nuts and carbonated drinks (p>0.05). Of the 441 students with acne, 247 (56%) had not sought any medical attention.

Conclusion: Acne vulgaris impacts the quality of life similarly to psoriasis, atopic eczema, and chronic urticaria. In mild acne cases, the quality of life may be significantly affected. Therefore, acne education is required in high schools and colleges to ensure that students understand their disease and are aware of available treatments.

INTRODUCTION

Acne vulgaris is common and occurs most frequently in adolescents and young adults. It is characterised by recurrent papules, pustules and nodules on the face, neck and upper trunk. The severity of skin involvement varies from mild involvement to disfiguring, which can negatively impact mood, self-esteem and quality of life. The estimates of acne prevalence vary from 35% to over 90% of adolescents, as reported by Stathakis et al.[1] Collier et al conducted a survey of 1013 participants in Alabama aged 20 years and older, in which 73.3% (n=744) reported ever having acne.[2] Wolkenstein et al., conducted a cross-sectional population-based online survey of 10,521 participants in seven European countries and reported an acne prevalence of 57.8%.[3] Hanisah et al., conducted a study of 409 secondary school students in Muar and reported an acne prevalence of 67.5%.[4] The prevalence of acne among 361 medical students at the Universiti Kebangsaan Malaysia was 68.1%, as reported by Muthupalaniappen et al.[5]

Acne vulgaris can result in significant psychological morbidity. Low self-esteem, anxiety, embarrassment or even depression related to the skin condition or disfiguring scars can have a substantial impact on the social life of the affected individuals.[6]

Sarawak is a state in East Malaysia, with a population of 2.4 million people, comprising 40 ethnic groups. Iban (36%), Chinese (21.7%), Malay (22.3%) and Bidayuh (8%) make up the majority of the population. To date, there is no local study or data on the prevalence of acne in Sarawak.

In this study, our primary objective was to assess the prevalence of acne and its psychosocial impact among high school and university students in Kuching, Sarawak. Secondary objectives included the assessment of the clinical characteristics of acne and its possible predisposing factors.

This article was accepted: 18 May 2022
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MATERIALS AND METHODS

This cross-sectional study was conducted in two secondary schools and two universities in Kuching. The study period was from November 2020 to November 2021. Ethical approval was obtained from the Malaysian Research and Ethics Committee (MREC). Inclusion criteria were students aged 16 to 25 years. The selection of two schools and two universities were based on cluster sampling. The study has two types of clusters which are schools and universities from Kuching. The two schools were selected randomly out of 40 schools and the two universities were selected randomly out of 16 universities/colleges in Kuching. The study sample was selected by a stratified cluster sampling method based on their academic years. Students were selected randomly using simple random sampling for each academic year. The selected students and their parents received an informed consent letter outlining the research. Students were excluded from the study if they or their parents refused consent or if they were absent during the day of the data collection.

The calculation of sample size was performed using the Epi Info Statistical Calculator. The minimum sample size calculated was 334, with an expected frequency of 68%[4,5] and a confidence level of 95%. Data were processed using Microsoft Excel and SPSS statistics software version 17. Numerical variables were described using mean ± standard deviation (SD). Nominal variables were described using frequencies and percentages. The correlation of two nominal variables was analysed using the chi-square test. Statistical significance was taken at a p-value <0.05.

A representative sample of high school and university students aged 16 to 25 years was examined by a team of dermatology-trained doctors to identify acne vulgaris. The diagnosed cases of acne were evaluated using the Dermatology Life Quality Index (DLQI). The students were also assessed clinically for disease severity by the principal investigator or coinvestigators. The severity of acne was graded using the Global Acne Grading System (GAGS).[7] In addition, information on demographic variables, such as gender, age, weight, height and type of acne lesions, and possible predisposing factors were recorded. Students were asked to recall diet history on the intake of milk, carbonated drinks, chocolate, sweets, potato chips, ice cream, fried chicken, yoghurt and nuts in the previous four weeks. The frequency of food intake was defined as 'seldom' (none to once a week) versus 'often' (twice or more per week). The frequency of drinks was defined as 'seldom' (none to 1 glass daily) versus 'often' (2 glasses daily or more). The concept of a diet questionnaire was adopted from Halvorsen et al.,'s study.[8] In addition, students were asked to recall their sleep history in terms of insomnia, duration, and timing of sleep for the past month. Frequent insomnia was defined as two times or more per week.

In 1997, Doshi et al., devised the GAGS.[9] This system divides the face, chest and back into six regions (forehead, each cheek, nose, chin, chest and back) and assigns a factor to each area (1: chin/nose, 2: cheek/forehead, and 3: chest/upper back) on the basis of surface area, distribution and density of pilosebaceous units. Each region is graded with a severity scale of 0 to 4 (0: no lesion, 1: comedones, 2: papule, 3: pustule, and 4: nodule), with the most severe lesion determining the local score. The local score for each region is the product of the severity score multiplied by the area factor. The global score is the sum of all the six local scores, with a minimum score of 0 and a maximum score of 44. The global scores of 1-18, 19-30, 31-38 and >39 are considered mild, moderate, severe and very severe, respectively.

DLQI is a validated questionnaire developed by Finlay et al., in 1994.[10] It contains ten questions that measure symptoms and feelings (questions 1 and 2), daily activities (questions 3 and 4), leisure (questions 5 and 6), work/school (question 7), personal relationships (questions 8 and 9) and treatment (question 10). Each question has four alternative responses: 'not at all', 'a little', 'a lot' or 'very much', with corresponding scores of 0, 1, 2 and 3, respectively. The answer 'not relevant' is scored as '0'. The DLQI score is calculated by summing the scores of each question (0-3), resulting in a maximum of 30 and a minimum of 0. A score of 0-1 signifies no effect on the quality of life, 2–5 signifies small effect on the quality of life, 6-10 signifies moderate effect on the quality of life, 11-20 signifies very large effect on the quality of life and 21-30 signifies extremely large effect on the quality of life.

RESULTS

A total of 582 students aged 16 to 25 years participated in this study. The mean age of the study population was 20.2 years (SD 2.7). There were 199 (34.2%) male and 383 (65.8%) female participants included in this study, giving a male:female ratio of 1:1.9. The demographic and clinical characteristics of the subjects are outlined in Table I. The overall prevalence of acne vulgaris was 75.8% (n=441). Of the 441 students with acne, 151 (34.2%) were males and 290 (65.8%) were females; 51.7% were Chinese, 18.4% Malays, 11% Iban, 7.9% Bidayuh, 4.1% Melanau, 0.9% Indians and 8.2% others (Bajau, Bisaya, Bugis, Dusun, Kadazan, Kenyah, Lun Bawang, Murut, Penan and Runggus). The mean age for students with acne was 19.9 years (SD 2.7). The mean body mass index (BMI) of the study population was 22.5 kg/m^2 (SD 7.9) with the majority of the participants (59.3%) being in the normal BMI category. The mean BMI for students with acne was 22.6 kg/m2 (SD 8.8), whereas the mean BMI for non-acne students was 22.2 kg/m^2 (SD 4.5). There was a significantly higher proportion of students with acne in the age group of 16-18 years than those without acne (37.4% versus 19.9%, p-value 0.001, Table I). The prevalence of acne was highest in the age group of 16-18 years and decreased with increasing age (Table II). On the other hand, there was no significant association between the presence of acne and gender, ethnicity or BMI (p>0.05).

Of those 441 students who had acne, 409 (92.7%) were classified as having mild acne with a GAGS score of 1-18, 30 (6.8%) were classified as having moderate acne with a GAGS score of 19-30 and two (0.5%) were classified as having severe acne with a GAGS score of 31-38. Of the 165 students aged 16-18 years, 152 (92.1%) had mild acne, 13 (7.9%) had moderate acne, and none had severe acne. Of the 180 students aged 19-22 years, 168 (93.3%) had mild acne, 10 (5.6%) had moderate acne and two (1.1%) had severe acne. Of the 96 students in the age group of 23-25 years, 89 (92.7%) had mild acne, 7 (7.3%) had moderate acne and none had severe acne. There was no significant association between the

Table I: Demography and clinical characteristics of study participants

Demography Characteristics		Acne n=441(75.8%)	No Acne n=141(24.2%)	Total	*p*-value
Gender, n (%)	Male	151 (34.2)	48 (34.0)	199 (34.2)	0.966[a]
	Female	290 (65.8)	93 (66.0)	383 (65.8)	
Ethnicity, n (%)	Malay	81 (18.4)	30 (21.3)	111 (19.1)	0.072[b]
	Chinese	228 (51.7)	53 (37.6)	281 (48.3)	
	Indian	4 (0.9)	3 (2.1)	7 (1.2)	
	Iban	47 (11.0)	17 (12.1)	64 (11.0)	
	Bidayuh	30 (7.9)	16 (11.3)	46 (7.9)	
	Melanau	18 (4.1)	7 (5.0)	25 (4.3)	
	Others	33 (8.2)	15 (10.6)	48 (8.2)	
Age (years), mean (SD)		19.9 (2.7)	20.8 (2.6)	20.2 (2.7)	\
Age Group, n (%)	16 to 18	165 (37.4)	28 (19.9)	193 (33.2)	0.001[a]
	19 to 22	180 (40.8)	71 (50.4)	251 (43.1)	
	23 to 25	96 (21.8)	42 (29.8)	138 (23.7)	
BMI, n (%)	Underweight	85 (19.3)	27(19.1)	112 (19.2)	0.914[a]
	Normal	262(59.4)	83 (58.9)	345 (59.3)	
	Overweight	70 (15.9)	25 (17.7)	95 (16.3)	
	Obese	24 (5.4)	6 (4.3)	30 (5.2)	
Acne Severity n (%)	Mild (GAGS 1–18)	409 (92.7)	–	–	
	Moderate (GAGS 19–30)	30 (6.8)	–	–	
	Severe (GAGS 31–38)	2 (0.5)	–	–	
	Very Severe (GAGS >38)	0 (0.0)			
Mean DLQI score (SD)	Mild Acne	4.0 (4.0)	–	–	
	Moderate Acne	7.1 (5.5)	–	–	
	Severe	15.5 (6.4)	–	–	

[a]Chi-square test.
[b]Fisher's exact test.

Table II: Prevalence of acne by age group

	16–18 years N=193	19–22 years N=251	23–25 years N=138	Total N=582
Number with acne	165	180	96	441
Prevalence	85.5%	71.7%	69.6%	75.8%

Table III: Acne impact on the quality of life and acne severity

Acne severity	Acne Impact on the Quality of Life				
	No DLQI 0–1	Small DLQI 2–5	Moderate DLQI 6–10	Very Large DLQI 11–20	Extremely Large DLQI 21–30
Mild, n (%) GAGS 1–18	147 (97.4%)	138 (93.9%)	90 (89.1%)	34 (82.9%)	0 (0.0%)
Moderate, n (%) GAGS 19–30	4 (2.6%)	9 (6.1%)	11 (10.9%)	5 (12.2%)	1 (100%)
Severe, n (%) GAGS 31–38	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.9%)	0 (0.0%)
Total	151 (100%)	147 (100%)	101 (100%)	41 (100%)	1 (100%)

Table IV: DLQI score with respect to gender and age group

DLQI Domains	Gender		*p*-value	Age Group			*p*-value
	Male Mean DLQI (SD)	Female Mean DLQI (SD)		16 –18	19–22	23–25	
Symptoms and feelings	2.4 (1.4)	2.4 (1.3)	0.803	2.1(1.2)	2.5 (1.4)	2.7 (1.2)	0.004
Daily activities	0.6 (1.0)	0.8 (1.0)	0.197	0.5 (0.9)	0.9 (1.1)	0.8 (1.1)	0.016
Leisure	0.8 (1.2)	0.9 (1.1)	0.396	0.6 (1.0)	1.0 (1.2)	1.0 (1.2)	0.002
Work and school	0.4 (0.7)	0.6 (0.9)	0.035	0.4 (0.8)	0.5 (0.8)	0.6 (0.9)	0.168
Personal relationship	0.3 (0.8)	0.5 (0.8)	0.049	0.3 (0.6)	0.5 (0.8)	0.5 (0.8)	0.010
Treatment	0.3 (0.7)	0.3 (0.7)	0.796	0.2 (0.6)	0.4 (0.8)	0.3 (0.6)	0.183

Table V: Diet, Sleep, and Acne

	Acne n (%)	No Acne n (%)	p-value
Milk			0.057
Seldom	219 (49.7)	83 (58.9)	
Often	222 (50.3)	58 (41.1)	
Carbonated drinks			0.352
Seldom	314 (71.2)	106 (75.2)	
Often	127 (28.8)	35 (24.8)	
Potato chips			0.169
Seldom	342 (77.6)	117 (83.0)	
Often	99 (22.4)	24 (17.0)	
Ice cream			0.291
Seldom	353(80.0)	107 (75.9)	
often	88(20.0)	34 (24.1)	
Chocolate			0.791
Seldom	364 (82.5)	115 (81.6)	
Often	77 (17.5)	26 (18.4)	
Sweets			0.932
Seldom	277 (62.8)	88 (62.4)	
Often	164 (37.2)	53 (37.6)	
Fried chicken			0.960
Seldom	221 (50.1)	71 (50.4)	
often	220 (49.9)	70 (49.6)	
Yogurt			0.601
Seldom	380 (86.2)	119 (84.4)	
Often	61 (13.8)	22 (15.6)	
Nuts			0.110
Seldom	381 (86.4)	114 (80.9)	
Often	60 (13.6)	27 (19.1)	
Sleep quality			0.884
Sleep less than 6 hours	197 (44.7)	62 (44.0)	
Sleep more than 6–8 hours	244 (55.3)	79 (56.0)	
Slept after 12 midnight			0.002
Yes	203 (46.0)	44 (31.2)	
No	238 (54.0)	97 (68.8)	
Frequent insomnia			0.011
Yes	51 (11.6)	6 (4.3)	
No	390 (88.4)	135 (95.7)	

age group and the severity of acne (p>0.05). Based on the local score of GAGS for each region, the most affected areas were the right and left cheeks with mean local scores of 2.5 (SD 1.7) and 2.4 (SD 1.8), respectively, followed by the forehead 2.0 (SD 1.6), chest/upper back 1.3 (SD 2.4), chin 0.7 (SD 0.9) and nose 0.4 (SD 0.7). Of the 409 students with mild acne, 133 (32.5%) were males and 276 (67.5%) were females. Of the 30 students with moderate acne, 16 (53.3%) were males and 14 (46.7%) were females. Of the two students with severe acne, all (100%) were males. There was a significantly higher tendency for male students to have moderate to severe acne (p=0.010).

In our study, the mean DLQI score for the students with acne overall was 4.3 (SD 4.3). The mean DLQI score was 4.0 (SD 4.0) for those with mild acne, 7.1 (SD 5.5) for those with moderate acne and 15.5 (SD 6.4) for those with severe acne. The correlation coefficient between GAGS and DLQI is significant at 0.322 with a p<0.001. Correlation analysis was conducted using Spearman's correlation test.

Of the 441 students with acne, 290 (65.8%) students had various impairments on the quality of life and 151 (34.2%) students had no impact on the quality of life. A DLQI score of 0-1 was defined as having no impact on the quality of life. The impact of acne on the quality of life was found to be small in 147 (33.3%) students with a DLQI score of 2-5, moderate (DLQI 6-10) in 101 (22.9%) students, very large (DLQI 11-20) in 41 (9.3%) students and extremely large (DLQI 21-30) in one (0.2%) student. The relationship between acne impact on the quality of life and acne severity is outlined in Table III. There was a significant association between the impact on the quality of life and acne severity (p<0.001). Increasing acne severity had a tendency to have a higher impact on the quality of life.

The mean DLQI score was 3.48 (SD 4.4) for male students, and it was 4.7 (SD 4.2) for female students. Of the male students with acne, no impact on the quality of life was found in 70 (46.4%) students, a small impact on the quality of life in 49 (32.5%) students, a moderate impact on the quality of life in 20 (13.2%) students, a very large impact on the quality of life in 11 (7.3%) students and an extremely large impact on the quality of life in 1 (0.7%) student. Of the female students with acne, there was no impact on the quality of life in 81 (27.9%) students, a small impact on the quality of life in 98 (33.8%) students, a moderate impact on the quality of life in 81 (27.9%) students and a very large impact on the quality of life in 30 (10.3%) students. A significantly higher proportion of female students had an impaired quality of life (p<0.001) compared to male students.

The most affected DLQI domain was 'Symptoms and feelings' with a mean DLQI score of 2.4 (SD 1.3), and the least affected DLQI domain was 'Treatment' with a mean DLQI score of 0.3 (SD 0.7). The mean DLQI scores of the domains of 'Daily activities', 'Leisure', 'Work and school' and 'Personal relationship' were 0.7 (SD 1.0), 0.9 (SD 1.2), 0.5 (SD 0.8) and 0.4 (SD 0.8), respectively. In comparison to male students, the mean DLQI scores were significantly higher in female students in the domains of 'Work and school' and 'Personal relationship' ($p<0.05$). However, there was no significant difference between male and female students in the DLQI domains of 'Symptoms and feelings', 'Daily Activities', 'Leisure' and 'Treatment' ($p>0.05$, Table IV). The mean DLQI scores for the age groups of 16-18 years, 19-22 years and 23-25 years were 3.0 (SD 3.5), 5.0 (SD 4.5) and 5.0 (SD 4.6), respectively. The mean DLQI scores were significantly lower in the age group of 16-18 years in the domains of 'Symptoms and feelings,' 'Daily activities,' 'Leisure' and 'Personal relationship' compared to the other age groups, as shown in Table IV ($p<0.05$). On the other hand, there was no significant difference among the age groups in the DLQI domains of 'Work and school' and 'Treatment' ($p>0.05$, Table IV).

There was no significant association of acne vulgaris with dietary intakes, such as chocolates, sweets, potato chips, yoghurt, milk, fried chicken, ice cream, nuts and carbonated drinks ($p>0.05$, Table V). There was a significantly higher proportion of students who had frequent insomnia in the group of students with acne compared to those without acne (11.6% vs. 4.3%, $p=0.011$, Table IV). A significantly high proportion of students who slept after midnight was also noted in the group of students with acne (46% vs. 31.2%, $p=0.002$, Table V). However, no association was found between acne severity, insomnia, duration and timing of sleep ($p>0.05$).

Of the 441 students with acne, 247 (56%) had not sought any medical attention, 165 (37.4%) self-purchased over-the-counter treatment from the pharmacy, 15 (3.4%) received spa treatment from beauticians and 14 (3.2%) received treatment from medical practitioners. Of the 409 students with mild acne, 229 (56%) had not sought any medical attention, 155 (37.9%) self-purchased over-the-counter treatment from the pharmacy, 12 (2.9%) received spa treatment from beauticians and 13 (3.2%) received treatment from medical practitioners. Of the 30 students with moderate acne, 16 (53.3%) had not sought any medical attention, 10 (33.3%) self-purchased over-the-counter treatment from the pharmacy, 3 (10%) received spa treatment from beauticians and 1 (3.3%) received treatment from medical practitioners. Of the two students with severe acne, none had sought any medical attention.

DISCUSSION

Acne vulgaris is a prevalent skin disorder that mostly affects teenagers and young adults. This study confirms that acne is a common skin problem in adolescents and young adults in Kuching, involving 441 students with an overall prevalence of 75.8%. Alajlan et al., reported an acne prevalence of 55.5% among medical students in King Saud University of Saudi Arabia.[11] The prevalence of acne was 34.7% among secondary schools in Egypt, as reported by Tayel et al.[12] In Korea, an acne prevalence of 71.2% was reported among high school students.[13] Comparisons of prevalence rates between studies are complicated by the fact that different studies employ a variety of different methods for grading acne and conducting studies. There are currently around 25 acne grading systems in use. However, there is no gold standard or standardised method that is routinely utilised in clinical practice.[14] For instance, in the study conducted by Muthupalaniappen et al., the definition of acne was a clinical diagnosis by the investigators and the Comprehensive Acne Severity Scale was used to characterise acne severity.[5] On the other hand, in the study done by Alajlan et al., the definition of acne was self-reported acne by the students.[11] Tayel et al., reported both the prevalence of self-reported acne and clinically proven acne in their study (34.7% and 24.4%, respectively), with the GAGS and the Cardiff Acne Disability Index being used to assess the acne severity.[12]

In our study, the prevalence of acne was highest (85.5%) in the age group of 16-18 years and decreased with increasing age. This finding was consistent with the study done by Wolkenstein et al.,[3] which showed the highest acne prevalence of 65.8% for the age group of 15-17 years and decreased with increasing age. Although acne can remain into adulthood, its prevalence tends to peak in adolescence and then decline.[3] The inverse relationship between age and acne in the current study was consistent with this pattern. The results of studies examining the association between acne vulgaris and weight have been mixed, leaving the relationship between these two conditions unclear. Obesity is usually related to peripheral hyperandrogenism, which can result in increased sebum production and the development of severe acne. Tsai et al reported that a higher BMI is a substantial risk factor for the development of acne in school children.[15] In contrast, Snast et al., reported that there was an inverse association between obesity and acne.[16] As the BMI increased, the chance of acne reduced significantly. In our current study, there was no significant association of acne with BMI.

Acne vulgaris has been shown to have a significant emotional impact on individuals. Embarrassment and low self-esteem associated with the appearance of the skin or the presence of a disfiguring acne scar can significantly influence the academic and social life of those who are affected.[17] Acne has been predicted to have psychological consequences comparable to those of other chronic conditions, such as asthma, epilepsy, diabetes or arthritis.[18] In this study, a significant proportion of 290 (65.8%) students with acne had an impaired quality of life. A very large impact on quality of life with a DLQI score of 11-20 was seen in 41 (9.3%) students. On the other hand, an extremely large impact with a DLQI score of 21-30 was seen in one (0.2%) student. In our study, the mean DLQI score for all the acne students was 4.3 (SD 4.3). This was comparable to a study done by Đurović et al.,19 which showed a mean Children's Dermatology Life Quality Index score of 4.3 (SD 5.1) among all acne students, whereas a mean DLQI score of 4.1 (SD 4.5) was reported in Yap's study.[20] The most affected DLQI domain was 'Symptoms

and feelings' with a mean DLQI score of 2.4 (SD 1.3). In comparison with male students, the mean DLQI scores were significantly higher in female students in the domains of 'Work and school' and 'Personal relationship' ($p<0.05$). Furthermore, there was a significantly higher proportion of female students who had an impaired quality of life ($p<0.001$). Female students had a higher total mean DLQI score of 4.7 (SD 4.2), despite the fact that male students had a higher tendency to have moderate to severe acne in our study ($p=0.010$). Males are more likely to suffer from severe acne than females. According to a previous study by Koku Aksu et al, there was a strong correlation between having severe acne and being male.[21]

In our study, females experienced a greater impact on the quality of life than males. The difference in study findings between male and female students suggested that females may experience a more significant psychosocial impact from acne than males, more likely due to females' higher level of cosmetic concern, higher perception of appearance and greater reliance on social relationships.[22] According to Do et al, females were more likely than males to have psychosocial disturbances in terms of self-perceived stress, social connections, peer relationships and self-esteem.[23] Wisuthsarewong et al., reported that females displayed a substantially larger loss of self-confidence and anxiety about physical appearance than males.[24] In addition, several studies have revealed that girls are more vulnerable to the negative psychological impacts of acne than boys.[25,26] However, Hanisah et al., reported that there was no significant difference in acne impact on the quality of life between genders among secondary school students in Muar.[4] This study demonstrated a weak to moderate positive correlation between the scores of DLQI and GAGS (p-value $p<0.001$). This result was consistent with the study done by Tatliparmak et al., which also demonstrated a positive correlation between the scores of GAGS and DLQI.[27] Safizadeh et al., reported that there was a weak to moderate positive correlation between the scores of GAGS and DLQI.[28] However, there was no correlation between the scores of GAGS and DLQI in a study done by Alsulaimani et al.[29] This implies that the severity of acne does not always correlate with the severity of psychosocial impact. Even mild acne can have a substantial emotional impact on patients. In this study, there were 41 students who had a very large impact on the quality of life and 34 (82.9%) of them had mild acne (Table III). This demonstrates the significance of the dermatologist's role in customising medical treatment to each patient's unique requirements in terms of quality of life. The mean DLQI score of 15.5 (SD 6.4) for severe acne is equivalent to those of debilitating dermatological conditions, such as atopic eczema, chronic urticaria, occupational contact dermatitis and psoriasis.[30,31,40] The impact of acne on the quality of life must be considered when treating acne. In our study, the mean DLQI scores were significantly lower in the age group of 16-18, especially in the domains of 'Symptoms and feelings', 'Daily activities', 'Leisure' and 'Personal relationship', in comparison with the other age groups. Students above the age of 18 felt that acne had a greater impact on their life than those below the age of 18. This finding was consistent with that of Wisuthsarewong's.[24]

The role of dietary variables in acne manifestation has been highly disputed. Studies that investigated the effect of various dairy products (including ice cream, yoghurt, cheese and various types of milk) on the appearance of acne yielded disparate results. The majority of research studies indicated that taking cheese, yoghurt, nuts, ice cream, fast food and carbonated drinks had no effect on acne risk. On the other hand, the effect of milk and chocolate/sugar consumption on acne risk was unclear, with contradictory results among trials.[32–35] Sleep deprivation may result in an increase in proinflammatory cytokines, which are often out of balance in acne. Sleep is also critical for poststress and postinflammatory healing. As a result, sleep deprivation could exacerbate skin conditions.[36] It was shown by a research team in France that there was a significant positive relationship between acne and fatigue upon awakening (poor sleep quality). In addition, it was discovered that stressed individuals experienced more fatigue upon waking and were more prone to develop acne.[37,38] Despite the fact that acne causes significant psychological morbidity, many adolescents believe that acne is a skin problem caused by poor cleanliness.[39] Embarrassment, stigma and misunderstandings regarding acne are the most common reasons that discourage adolescents from seeking help. The majority of our students with acne (56%) did not seek any medical attention. This may imply that there was a lack of awareness of acne and its possible treatment to reduce its psychosocial impact.

LIMITATION

The cross-sectional design of this study is its major limitation. The cross-sectional design of the study means that although associations can be identified, causality cannot be demonstrated. A prospective study would be preferable to show a direct causal link between acne, quality of life, and its risk factors. Students who refused to participate or were absent might have been more susceptible teenagers or young adults who were most embarrassed by their skin.

CONCLUSION

Acne vulgaris has a similar effect on the quality of life as psoriasis, atopic eczema and chronic urticaria. There was a weak to moderate correlation between the scores of GAGS and DLQI. A significant impact on the quality of life may be seen in mild-acne cases. Thus, all patients with acne vulgaris must have their quality of life addressed. Acne should be viewed by health care practitioners as a psychologically debilitating condition that requires optimal management. Acne education is necessary in our high schools or universities to ensure that students understand their disease and are aware of potential treatments. The lack of awareness of good treatment options in the management of acne needs to be emphasized. Those with a significant impact on the quality of life due to acne should be made aware of the care available with both primary care practitioners and dermatologists in ensuring successful wholesome management of acne.

ACKNOWLEDGEMENT
We would like to thank the Director General of Health Malaysia for his permission to publish this article. We are also grateful to the Sarawak Education Department for allowing us to conduct the study in schools.

FUNDING
This study is self-funded.

CONFLICT OF INTEREST
There is no conflict of interest.

ETHICAL APPROVAL
Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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ORIGINAL ARTICLE

Characteristics, symptom management and outcomes in Covid-19 patients referred to palliative care in a tertiary hospital

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) variants pose unique challenges with inevitable premature death when cases of severe disease exponentially rise in a healthcare system. It is imperative that palliative care is provided with a proactive approach to symptom recognition, assessment, management and treatment escalation to ensure comfort throughout the course of this illness.

Objectives:To evaluate the characteristics, symptom burden, palliative care management and outcomes of COVID-19 patients referred to a palliative care unit (PCU) in a single tertiary hospital. Clinical outcomes specifically observed the management of agitation in these patients based on their Richmond Agitation and Sedation Scale (RASS) scores.

Methods: A retrospective observational study was conducted in a tertiary hospital by reviewing electronic medical records and extracting data from 1st June 2021to 31st July 2021 of all COVID-19 patients referred to the PCU.

Results: A cohort of 154 (75 males, 79 females) COVID-19 patients was referred to the PCU with a mean age of 67 (20-95) years. The median number of days of COVID-19 illness before referral was 7(4-11), with 79.3% of patients being in categories 4 and 5. The median duration of the PCU involvement was 4(1-24) days; 74% of families were engaged in virtual platform communication. The most prevalent symptoms were dyspnoea (73.4%) and agitation (41.6%). Common medications used were opioids, antipsychotics and benzodiazepines. Among agitated patients, none had RASS scores above +2 in the last encounter. Palliative care doctors in the team reported complete effectiveness in patient's symptom control in 74% of patients.

Conclusions:A hallmark of severe COVID-19 is rapid deterioration, which calls for proactive assessment and urgent palliation. Breathlessness and agitation are priority symptoms to address. Among agitated patients, benzodiazepines and antipsychotics are highly effective in addressing agitation and reducing RASS scores. Communication with families using virtual platforms is effective in providing a supportive presence and closure when face-to-face communication is not possible.

KEYWORDS:
COVID-19, palliative care, symptom management, RASS

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported to the World Health Organization (WHO) on 31st December 2019.[1] By 30th January 2020, the WHO Director-General had declared the COVID-19 outbreak a public health emergency of international concern, WHO's highest level of alarm.[1]

The emergence of COVID-19 variants of concern[2-6] has brought upon a deadlier disease in terms of its transmission and its disease severity. Its high transmissibility has led to an exponential rise in the number of cases in Malaysia and globally. This surge posed unique challenges[7] to healthcare systems in terms of the extraordinary and sustained demands on public health and healthcare systems, resulting in the need to ration medical equipment and interventions.[8] The unfortunate reality of healthcare systems being overwhelmed by large waves of COVID-19 is that it leads to premature death due to limitation of resources and inequitable healthcare provision. Therefore, while every effort should be made to prevent such inequitable care, it is imperative that palliative care is always provided to alleviate the suffering of these patients.[9-11]

Malaysia has so far experienced its most deadly wave of the COVID-19 pandemic, beginning in May 2021, when the numbers of deaths increased rapidly, reaching its peak in the months of July and August 2021. At its peak, the COVID-19 in-patient burden reached up to 2799 hospital admissions and up to 290 deaths within a single day.[12] Of these cases, over 1/3 were in the Klang Valley and the central state of Selangor Darul Ehsan. During this time, palliative care services were called upon to help provide the best care possible for patients with severe COVID-19 in the face of limited resources and high mortality risk.

International reports[13] have found that patients referred for palliative care were of older ages with higher rates of comorbidities, reflecting global data on COVID-19 mortality risk. The time spent under palliative care was short with a significantly high mortality rate.[14] Not surprisingly, this is consistent with the disease trajectory, as evident by its rapid deterioration[15] to mortality. The main symptoms[13,14,16] encountered were dyspnoea, followed by agitation, drowsiness, pain, delirium, respiratory secretions, cough and fever. The route of administration of medications to manage symptoms was mainly through continuous subcutaneous infusion (CSCI). Pharmacological medication used for

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symptom control was opioids for dyspnoea,with morphine being the most commonly used opioid.[17,18] The median dose of subcutaneous morphine of 10mg–15mg/day was required to address dyspnoea.[14,16] Alfentanil or fentanyl was used for patients with renal impairment for dyspnoea. Addressing symptoms of restlessness and agitation coupled with a short imminent dying phase proved to be very challenging for healthcare workers. Benzodiazepines were found to be useful in addressing agitation.[13,16] The assessment of clinical outcomes in terms of the overall condition of patients was determined by clinical impressions of effectiveness.[13,16]

With regard to assessing levels of agitation in patients with COVID-19, there is a lack of objective assessment tools available in the existing literature. The Richmond Agitation and Sedation Scale (RASS), however, is an instrument designed to assess the level of alertness and agitated behaviour in critically ill patients. It helps to establish simple and discrete criteria for assessing arousal and agitation and can be useful to guide sedation therapy to address agitation in COVID-19 patients.

Another important aspect in caring for critically ill patients with COVID-19 is communication. It is challenging to deliver effective communication in COVID-19 isolation wards as health professionals will be speaking to patients under layers of personal protective equipment, which muffles voices and obscures nonverbal cues.[19] Emerging evidence supports the use of video consultations with patients and family members as an effective, accessible, and acceptable method of communication.

In this retrospective observational study, we seek to evaluate the characteristics, symptom burden, palliative care management and outcomes of COVID-19 patients from the experience of a palliative care unit (PCU) in a single tertiary hospital in Malaysia. Clinical outcomes specifically observed the management of agitation and delirium in these patients based on their RASS scores. We also sought to evaluate the utility of virtual platform communication in managing these patients.

MATERIALS AND METHODS

This is a retrospective observational study that was conducted in Hospital Selayang, a tertiary hospital located in the state of Selangor Darul Ehsan, Malaysia. Hospital Selayang became an acute fully COVID-19 hospital, which was designated to exclusively manage COVID-19 infected patients during the peak pandemic period from June 2021 until September 2021. High-risk groups of patients withCOVID-19 would be admitted to isolation wards regardless of their illness category, and those deemed to have a high risk of mortality or who were inevitably dying from COVID-19 would be referred to the PCU.

Data were collected retrospectively for all patients aged more than 18 who were referred to the PCU from 1st June 2021 to 31st July 2021(8 weeks period). Patients confirmed with positive results from nasopharyngeal swab COVID-19 polymerase chain reaction tests were included.

Patients were identified from the referral system record of the PCU, and their electronic medical records, including medical notes, nursing notes, blood investigations and medication prescriptions, were reviewed. Variables included baseline demographics; comorbidities; palliative care phase of illness[20] (stable, unstable, deteriorating and terminal) upon the first review; category phase of COVID-19 illness; day of COVID-19 illness when patients received the first review by the palliative care team; days of palliative care team involvement; COVID-19-related end-organ damage; source of referral; outcomes of patients (death, post-COVID care ward and home); utilisation of virtual communication (via platforms of WhatsApp video call, Zoom meeting and Google Meet) with family members; and requirement for a family conference and goals of care (GOC) discussion were extracted from the records. Symptom burdens were identified, and drug delivery via different routes, such as per oral, CSCI and intravenous infusion, for symptom control with final doses used was recorded. Clinical efficacy on symptom control was sought based on clinical notes at the last encounter made by the palliative care team or primary team in charge.

Specifically, assessment of the RASS among agitated patients was recorded before and after medication was started to determine the effectiveness of symptom control. RASS is a 10-point scale, with four levels of anxiety or agitation (+1 to +4 [combative]), one level denoting a calm and alert state (0), and 5 levels of sedation (-1 to -5) culminating in unarousable (-5).

Data were analysed by SPSS version 26 (Armonk, NY). Descriptive statistics were presented as mean, medianand range in interval ratio variables. Nominal and ordinal variables were generated in frequency counts—n,%.

RESULTS

A total of 154 COVID-19 patients were referred to the palliative care team between 1st June and 31st July 2021. The mean age was 67 years (20-95) of which 54.5% (84) comprised of the Malay ethnic group, followed by 27.9% (43) Chinese and 13.0% (20) Indian patients. Among 154 patients, 81.6% (111) suffered from more than 1 comorbidity, with the most common comorbidities being hypertension (66%), diabetes mellitus (49.4%) and dyslipidaemia (26%).

In terms of the clinician-assessed palliative care phase of illness, 39.6% of our cohort was noted to be in the stable phase (no immediate symptom management required), whereas 31.2% were unstable (requiring immediate symptom control). The majority of patients were referred with category 4 (48.1%) or category 5 (38.3%) illness, meaning they were mostly requiring oxygen therapy with severe illness. The median time to referral was on day 7 [4-11] of illness. In this cohort of COVID-19 patients, 50% developed complications of acute kidney injury and 11% had transaminitis. The duration of palliative care involvement was noted to be relatively short, with a median duration of only 4 (1-24) days; 74.7% of patients passed away, whereas 7.8% of patients were transferred to a post-COVID care ward to continue care in the context of pulmonary rehabilitation and weaning down oxygen requirements (to a minimum level at 3L/min)

Table I: Demographics, clinical characteristics, palliative care phases, virtual communication involvement and clinical impression on drug effectiveness in COVID-19 patients referred to the palliative care team

Total Number of Palliative COVID-19 Patients	N=154
Age, mean (range) years	67 (20 - 95)
Gender; n (%)	
Male	75 (48.7)
Female	79 (51.3)
Ethnicity; n (%)	
Malay	84 (54.5)
Chinese	43 (27.9)
Indian	20 (13.0)
Others	7 (4.5)
Comorbidities; n (%)	
Hypertension	103 (66.0)
Diabetes mellitus	76 (49.4)
Dyslipidaemia	26 (16.9)
Ischemic heart disease	21 (13.6)
Cerebrovascular disease	20 (13.0)
End-stage kidney disease	17 (11.0)
Chronic kidney disease	17 (11.0)
Advanced malignancy	14 (9.1)
Congestive cardiac failure	7 (4.5)
Bronchial asthma	7 (4.5)
Chronic obstructive pulmonary disease	6 (3.9)
Atrial fibrillation	6 (3.9)
Obesity	4 (2.6)
Neurodegenerative disease	4 (2.6)
Connective tissue disease	3 (1.9)
Psychiatric illness	3 (1.9)
Pulmonary tuberculosis	1 (0.6)
Epilepsy	1 (0.6)
Others*	13 (8.4)
No known medical illness	18 (11.7)
Total comorbidities >1; n (%)	111 (81.6)
Palliative Care Phase (upon first review); n (%)	
Stable	61 (39.6)
Unstable	48 (31.2)
Deteriorating	32 (20.8)
Terminal	13 (8.4)
Category of COVID-19; n (%)	
1	1 (0.6)
2	5 (3.2)
3	15 (9.7)
4	74 (48.1)
5	59 (38.3)
Day of illness in COVID-19, median (range)	7 (4-11)
Days of palliative care involvement, median (range)	4 (1-24)
COVID-19-related end-organ damage; n (%)	
Acute kidney injury	77 (50.0)
Transaminitis	17 (11.0)
Referral Source; n (%)	
Ward	145 (94.2)
ED	7 (4.5)
ICU	2 (1.3)
Patient outcomes, n (%)	
Death	115 (74.7)
Post-COVID care ward	12 (7.8)
Home	27 (17.5)
Clinical impression of effectiveness	
Complete	114(74.0)
Partial	19 (12.3)
Unknown (patient died before follow up)	21 (13.6)
Involved virtual communication; n (%)**	
Yes	114 (74.0)
No	40 (26.0)
Discussion on GOC; n (%)	
Yes	131 (85.1)
No	23 (14.9)

n(%): number of patient(percentage).
ED: Emergency Department, ICU: Intensive Care Unit, GOC: Goals of Care
*Others: Knee OA, Paroxysmal nocturnal haemoglobinuria, Trisomy 21, Hypothyroid, Cerebral Palsy and Gout.
** Virtual communication in forms of WhatsApp video call, Zoom meeting,Google Meet, phone call.

Table II: Prevalence of symptoms and number of symptoms recorded per patient

Symptoms observed (in patients)	N (%)
Dyspnoea	113 (73.4)
Agitation	64 (41.6)
Cough	11 (7.1)
Respiratory Secretion	9 (5.8)
Fever	7 (4.5)
Pain	6(3.9)
Nausea/Vomiting	4 (2.6)
Others	10 (6.5)
Seizure	3
Myoclonic jerk	1
Insomnia	3
Itchiness	1
Haemoptysis/UGIB	2
Number of symptoms recorded per patient	N (%)
0	20(13)
1	52 (33.8)
2	71 (46.1)
3	10 (6.5)
4	1 (0.6)

UGIB: Upper gastrointestinal bleeding.

Table III: Frequency of drugs that were used during the first encounter and the last encounter

Drug Used	Drugs During the First Encounter N (%)	Drugs During the Last Encounter N (%)
Drugs given per oral		
Aq morphine PRN	8 (5.2)	11(7.1)
Aq morphine Regular	13 (8.4)	10 (6.5
Drugs given by s/c		
s/c Morphine prn	23 (14.9)	17 (11)
s/c Morphine regular	6 (3.9)	2 (1.3)
Drugs given by CSCI		
Fentanyl	37 (24)	31 (20.1)
Fentanyl + haloperidol	17 (11)	10 (6.5)
Fentanyl + midazolam	10 (6.5)	15 (9.7)
Morphine	7 (4.5)	2 (1.3)
Morphine + haloperidol	3 (1.9)	4 (2.6)
Morphine + midazolam	1 (0.6)	4 (2.6)
Midazolam alone	4 (2.6)	3 (1.9)
Fentanyl + midazolam + haloperidol	–	19(12.3)
Fentanyl + midazolam + haloperidol + buscopan	–	1 (0.6)
Fentanyl + buscopan	–	1 (0.6)
Fentanyl + levomepromazine	–	1 (0.6)
Morphine + haloperidol + midazolam	–	3 (1.9)
Drugs given by IVI		
IVI Fentanyl + midazolam	7 (4.5)	4 (2.6)
IVI Morphine + midazolam	3 (1.9)	3 (1.9)
Others**	15 (9.7)	13 (8.4)

Aq: aqueous, s/c: subcutaneous, CSCI: continuous subcutaneous infusion, IVI: intravenous infusion, PRN: when necessary (pro re nata).
** Others: Paracetamol, Bromhexine, TD Fentanyl, Tramadol, Lorazepam, None.

Table IV: Median dose of medication that were used during the first and the final titration doses

Drug Used	Drug Dose in 24hours: median, (range) [IQR] (initial starting dose)	Drug dose in 24hours: median, (range) [IQR] (last titrated dose)
CSCI Morphine (mg)	10	13 (10-20)
CSCI Fentanyl (mcg/hr)	6 (4-12)	12 (6-16)
CSCI Midazolam (mg)	10	10 (10-15)
CSCI Haloperidol (mg)	1 (1-2)	1 (1-2)
CSCI Buscopan (mg)	60	60
CSCI Levomepromazine (mg)	–	25

CSCI: continuous subcutaneous infusion, [IQR]: interquartile range

Table V: RASS score for patients with agitation during the first and the final encounters

RASS Score	First Encounter	Final Encounter
+3	19 (29.7)	–
+2	26 (40.6)	–
+1	7 (10.9)	–
0	5 (7.8)	3 (4.7)
–1	4(6.3)	16 (25)
–2	2 (3.1)	22(34.3)
–3	–	16 (25)
–4	1 (1.6)	7 (10.9)

** RASS: Richmond Agitation Agitation–Sedation Scale—It is a ; validated tool to assess the level of alertness and agitated behaviour in critically- ill patients. It Consist consist of 10-point scale, with four levels of agitation (+1 to +4 [combative]), one level to denoting a calm and alert state (0), and 5 levels of sedation (–1 to –5) culminating in unarousable (–5)

Box 1: Adapted from clinical management of confirmed COVID-19

Box 1: Adapted from clinical management of confirmed COVID-19	
Category 1	Asymptomatic
Category 2	Symptomatic, No Pneumonia
Category 3	Symptomatic, Pneumonia
Category 4	Symptomatic, Pneumonia, Requiring supplemental oxygen
Category 5	Critically ill with multiorgan involvement

Confirmed COVID-19 patients in Malaysia are classified into 5 categories as stated in box 1.

Box 2: Definition of Palliative Care Phases

Stable	Adequately controls existing problems and symptoms and plans further interventions to maintain symptom control and quality of life. Family and carer situation is relatively stable, and no new issues are apparent
Unstable	Existing problems rapidly increase in severity and/or New problem(s) develop that were not anticipated in the existing plan of care and/or Family and carer circumstances change that suddenly impact on patient care
Deteriorating	Overall functional status is declining and gradual worsening of existing problems and/or New, but anticipated, problems develop and/or Family and carers experience gradual worsening distress, which impacts patient care
Terminal	Death is likely within days The Palliative Care Phase is reliable and acceptable in a national study, aims to assist carers and healthcare professionals to assess, plan and care for patients with advancing life-limiting illness.

accordingly. Twenty-seven patients managed to discharge home without the need of oxygen support and no further need of specialist palliative care. Overall, the clinician's impression of the effectiveness of symptom control was reported as 74% (114) of patients with complete control of symptoms, 12.3% (19) with only partial control and 13.6% (21) died before clinical effectiveness could be determined.

A total of 74% of patients and family members were able to engage in discussions with the palliative care team using virtual communication platforms. GOC discussions with patients or families, if patients were unfit to participate, were required in 85.1% (131) of cases.

The prevalence of the symptoms (Table II) reported included dyspnoea 73.4% (113), followed by agitation 41.6% (64), cough 7.1% (11), fever 4.5% (7), pain 3.9% (6), nausea 2.6% (4) and others 6.5% (10). Among the symptom burdens, 53.2% (82) of patients had at least two or more symptoms and 33.8% (52) had one symptom, whereas 13% (20) of patients were noted to be asymptomatic.

A total of 51.3% (79) of patients were started on CSCI upon the first review for symptom control, and this increased to 61% (94) by the last encounter. In the cohort, during the last review, 70.1%(108) of patients required regular opioid therapy, with fentanyl being more commonly used (75.9%) compared to morphine (24.1%). The median (Table IV) starting dose for the s/c fentanyl and s/c morphine was 6mcg/h (interquartile range [IQR] 4mcg/h,12mcg/h) and 10mg/day, respectively. The median final titrated dose for s/c fentanyl was doubled to 12mcg/h (IQR 6mcg/h,16mcg/h), whereas for s/c morphine, it was 13mg/day (IQR 10/day,20/24h). The median dose of s/c midazolam was observed at 10mg/day (IQR 10/day,15/day).

Agitation was the second most common symptom with a total of 64 patients recording this symptom. Of these patients, 29.7% (19) had RASS scores of +3 and 40.6% (26) had RASS scores of +2 (Table V). During the last review, no patients were observed to have RASS scores suggesting agitation and restlessness.

DISCUSSION

This study describes the demographics, clinical characteristics, symptom management and delirium outcomes of COVID-19 patients referred to a palliative care team in a tertiary government hospital in Selangor, Malaysia. It provides a glimpse into the palliative care needs of patients with severe COVID-19 infections and a high risk of mortality during an acute surge of COVID-19 where the healthcare system is overwhelmed.

In our study, patients tend to be in their 60s, with a slight female preponderance, a significant level of functional impairment and a high burden of comorbidity.[12,21] Hypertension and diabetes were the most frequent comorbidities in our patients. The mean age of patient's referred to the palliative care team was lower than most international reports,[22] which may reflect the high prevalence of comorbidities,[23] such as diabetes mellitus and hypertension, as well as the lower life expectancy in Malaysia.[24]

Patients who were initially referred to the palliative care team were mostly in the stable phase (palliative care phase of illness), and this is in keeping with the Malaysian government health policy whereby all COVID-19 patients with conditions and comorbidities predisposing them to a high risk of clinical deterioration[25] must be admitted to a hospital. Although about 40% of patients seemed stable at first review, the final outcome, unfortunately, resulted in death for 74.7% of the cohort. This illustrates how the clinical course of this illness is indeed very acute, with rapid deterioration occurring over a period of short days. Another reason for this would be due to the occurrence of silent hypoxemia,[26] in which patients may appear clinically stable, whereas in actual fact, they are having a deteriorating respiratory function. Hence, when caring for patients with severe COVID-19, clinicians must always be vigilant to monitor patients for rapidly progressing symptom distress, as the duration of palliative care involvement tends to be brief and there is a narrow window of opportunity to ensure adequate comfort.

Given the rapid deterioration in our patient group, early identification of COVID-19 patients with poor prognostic factors is imperative to allow optimal palliative care, symptom management and support at the end of life.[27] The most common symptoms in our study were dyspnoea and agitation, followed by cough, respiratory secretions, fever, pain, nausea and vomiting. In terms of agitation, 70.3% scored +2 or more on the RASS scale, suggesting a severe degree of distress. In terms of symptom clusters, the majority of patients (53.2%) reported 2 or more symptoms, and therefore, the symptom burden is indeed high.

Another observation is that 61% of the patients reported COVID-19-related organ failure. This was mainly due to acute kidney injury, which was evident in 50% of patients, and acute transaminitis, involving 11% of patients. Kidney disease has been reported as a poor prognostic factor, which is associated with mortality in COVID-19.[19] This has significant implications, especially when considering the use of opioids, and explains why fentanyl was very commonly used in our setting.

Oral pharmacological management is the preferred route unless the patient is unconscious or when rapid titration of medications for symptom control is needed. CSCI was required in most cases, but with relatively low doses of opioids and benzodiazepines for effective symptom control, which is in keeping with other published reports.[14,16] Given the short duration of palliative care team involvement, we found that it is important that CSCIs be commenced promptly at conservative initial doses when the terminal phase is diagnosed in a patient with COVID-19 and the doses be titrated to effect. Although many patients required CSCI opioids and benzodiazepines because of their rapidly deteriorating condition and because fentanyl was frequently used, another reason why CSCI medications were commonly used is that it helped to reduce the need for nursing staff to repeatedly go in and out of isolation areas to provide 4 hourly injections. Although nursing staff had tried their best to provide medications on time, due to the overwhelming numbers of admissions to already crowded wards, this was far from optimal, and practical measures were required to provide the best care and comfort possible.

The pandemic has presented unique challenges for health services as efforts to limit the risk of infection to staff and patients are balanced against the need for communication and support for patients and their families. Recognising this, we embarked on the use of videoconferencing with smart devices for virtual interaction to allow communication between family, caregivers and patients. Communicating via video conferencing can enhance the 'therapeutic presence'[28,29] of healthcare professionals with family and caregivers as a new norm in this pandemic. It calls for urgent adaptation to tele-SPIKES in clinical practice to facilitate family conferences.[30-32] A good framework can be effective guidance to practitioners in virtual communication, especially in the context of COVID-19, which often faces numerous potential uncertainties. It emphasises on (1) Goals—discuss GOC and ask about expectations; and (2) Options—clarify current treatment options available with risks and benefits. To acknowledge potential uncertainties in the disease trajectory (3) Opinions—to elicit patients' preferences based on available options and to achieve shared decision-making; (4) Documentation—document the discussion on goals, options, opinions, preferences and care plan. Overall, 74% of patient and family discussions were conducted using a virtual platform, and this was found to be effective and acceptable in this study population.

The learning point in this retrospective study is effective symptom management of dyspnoea and agitation with standard doses of opioid and benzodiazepine in COVID-19. This study echoed similar findings with other literatures.[13,14,16] In fact, it reflects that palliative care is not limited to end-of-life care to ease physical suffering in COVID-19 with a short prognosis but symptom relief on dyspnoea among COVID-19 survivors, for example, while waiting for pulmonary rehabilitation. Nevertheless, it provides an insight into the preparedness for humanitarian crises in the future with palliative care philosophy. Access to palliative care is about human dignity and basic human rights. Let us leave no one behind for those in need but explicitly support them.

There are a number of limitations in this study, which first include the fact that it was a retrospective study using electronic medical record review, as the acute exponential rise in case numbers during this deadly wave of the pandemic did not allow for sufficient preparation to conduct a prospective study. Hence, the selection of patients referred to the PCU team after a detailed discussion between specialists and consultants was not captured in this study. Further studies in the future can be conducted prospectively with well-designed selection criteria for our unique patient population when limitation of resources is not present and to assess acceptability of PCU service from patients. Also, the study sample was small, from a single tertiary hospital located in urban Selangor; hence, the demographic characteristics and needs of patients may not be reflective of the entire Malaysian population. Our study included only patients referred to the PCU, and therefore, there is a lack of information about the palliative care needs of other inpatients with COVID-19 or patients from the community. We also did not collect data on symptom severity apart from looking at the RASS score.

Additional research work is required to look into the needs of other patients, including those in the community and those dying in hospitals who are not referred to the PCU. The assessment of response to medication was subjective, and as the length of palliative care involvement was relatively short, there was not always sufficient time to assess the effectiveness of treatments.

CONCLUSION

This study demonstrated our Malaysian experience of palliative care needs in patients with severe COVID-19. It also demonstrates the role of palliative care in such situations and how it can address symptom distress and alleviate suffering despite various challenges. Virtual communication platforms are indeed a useful and necessary approach to maintaining therapeutic relationships and a supportive presence in this 'new era' where physical distancing is unavoidable. It is important that such experience in handling severe COVID-19 will allow more preparedness in managing future pandemics with palliative care principles.

ACKNOWLEDGMENTS

The authors thank MOH Hospital Selayang for permission to conduct this study.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

FUNDINGS

The authors received no financial support for the research, authorship, and publication of this article.

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ORIGINAL ARTICLE

Propolis mouthwash for preventing radiotherapy-induced mucositis in patients with nasopharyngeal carcinoma: A randomized control trial

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Malaysia. The gold standard treatment of NPC is radiotherapy (RT), as NPC is a radiosensitive tumour. Although RT is successful in treating NPC, patients cannot avoid the resulting RT complications. Oral mucositis is the most frequently encountered debilitating complication of RT and has no specific preventive treatment. The aim of this study was to evaluate the efficacy and safety of a 2.5% propolis mouthwash for preventing RT-induced mucositis in patients with NPC.

Materials and methods: The study was a prospective, double-arm, randomised control trial with intervention. The patients were randomly divided into an experimental group receiving propolis mouthwash and a placebo group receiving normal saline mouthwash. All patients were instructed to rinse their mouths with 7mL mouthwash three times daily for six weeks. The severity of oral mucositis was then evaluated by the World Health Organization Oral Toxicity Scale at the second, fourth, and sixth weeks of the study.

Results: In total, 17 patients completed the study: 10 patients used the propolis mouthwash and seven used the placebo mouthwash. The mean mucositis scores for the propolis mouthwash compared to the placebo at the second, fourth, and sixth weeks were 0.10 vs. 1.14, 0.50 vs. 2.00, and 1.20 vs. 2.86, respectively, and the differences between the two groups were statistically significant (p<0.001).

Conclusion: A 2.5% propolis mouthwash was both safe and effective for reducing the severity of oral mucositis following RT for NPC.

KEYWORDS:
Nasopharyngeal carcinoma, radiotherapy, mucositis, propolis mouthwash

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common cancer of the head and neck in Malaysia and is the fifth most common of all cancers among all Malaysian residents.[1] The gold standard treatment for NPC is radiotherapy (RT), as NPC tumours are radiosensitive. The Malaysia Clinical Practice Guidelines recommend that stage I NPC be treated with definitive RT to the nasopharynx and elective RT to the neck region, whereas stage II, III, and IVa NPC should be treated with concurrent chemoradiotherapy (CCRT). Only palliative treatment is available for stage IVb NPC (distant metastasis). The RT dose for the primary tumour site is 66-70 Gray (Gy) at 33-35 fractions for 6-7 weeks, and 54-70 Gy at 30-35 fractions for 6-7 weeks for the neck region. If the neck nodes are negative, the neck region dose is 54-60 Gy for 30 fractions for six weeks. These RT can successfully treat NPC, but they leave the patients with serious complications from the RT itself. Oral complications, such as oral mucositis, dysphagia, and taste changes, are commonly experienced by patients with NPC undergoing RT.

RT-induced oral mucositis is the most common debilitating ionizing radiation toxicity arising from RT. It is a normal tissue injury after exposure to RT and lasts between 7 and 98 days, starting with acute inflammation of the oral mucosa, tongue, and pharynx. The epithelial cells of the oropharyngeal mucosal lining desquamate, leading to basement membrane damage, loss of the protective barrier, and then to ulceration and infection. RT-induced oral mucositis occurs in almost 80% of head and neck cancer patients who undergo RT.[2] The major consequences of RT-induced oral mucositis include hospital admission for pain management, total parenteral nutrition, and antibiotic administration in 62% of the patients, while 70% of the patients with grade 3 and 4 oral mucositis require feeding tube insertion. About 35% of the patients need to abandon their cancer protocol treatments due to the development of dose-limiting toxicity.[3] No specific treatment will prevent RT-induced oral mucositis, but good oral care is known to aid in reducing the severity of mucositis. The mainstay of effective oral care is mouth rinses, as these can help in sweeping away debris and keeping the oral mucosa clean and moist.

Many published studies have tested alternative natural product treatments for the prevention of oral mucositis. Common products considered as alternative treatments have

This article was accepted: 16 May 2022
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often been honey-based products, which have been deemed very efficient at preventing or reducing the severity of oral mucositis in patients undergoing cancer treatment.[4] In particular, stingless bee products are well known for their medicinal properties for treating numerous diseases.[5] The present study is the first in Malaysia to seek out alternative preventive treatments for oral mucositis using propolis from the stingless bee as a mouthwash.

MATERIALS AND METHODS

Study Design

This was a prospective, double-arm, randomised control trial (RCT) with intervention. Its aim was to determine the efficacy of a 2.5% propolis mouthwash in preventing RT-induced mucositis among patients with NPC attending the Otorhinolaryngology, Head, and Neck Surgery (ORL-HNS) clinic at the Advanced Medical and Dental Institute (AMDI), Bertam. The study was approved by the ethical committee of the Human Research Ethics Committee of Universiti Sains Malaysia (HREC) (JEPeM USM Code: USM/JEPeM/20010025) and was conducted from 1 April 2020 until 30 June 2021. The sample population was selected from patients diagnosed with NPC attending the ORL-HNS clinic at AMDI, Bertam, who met the inclusion and exclusion criteria. The inclusion criteria were all patients diagnosed with NPC scheduled to undergo CCRT. Exclusion criteria were allergy to bee products, NPC stage T1 N0 M0, and age younger than 18 years.

Methods

All NPC patients who attended ORL-HNS clinic AMDI, Bertam, were screened for eligibility. Consent to participate in the study was obtained after the purpose, importance, and benefit of the study were explained to the patients and necessary documentation was given to the patients for consultation and for references. The patients were randomly divided into an experimental and a placebo group by using ballot system. The experimental group was given a 2.5% propolis mouthwash, and the placebo group was given a normal saline mouthwash. All patients were provided with a pamphlet of instructions. The mouthwashes (propolis and saline) were provided by AMDI, Bertam, and were packaged in identical bottles labelled A and B.

The propolis was diluted in water at 60°C until it fully dissolved, and the volume was made up to 150mL for gargling. The solution was stored in a normal refrigerator to prevent fermentation of the propolis.

All patients were provided every week with a bottle of product containing 150mL of either 2.5% propolis or normal saline according to their respective groups. All the patients were instructed to rinse their mouths with 7mL (measured using syringe provided) of the assigned mouthwash for 60 seconds and then spit it out. This was done three times per day: on the RT days from Monday to Friday, the patients were instructed to perform the mouth rinse at 30 minutes before starting the RT, at 30 minutes after completing the RT, and then at 6 hours after the RT. During the rest days on Saturday and Sunday, the patients were instructed to rinse their mouths at specific times of 8 am, 3 pm, and 10 pm. These mouth rinses were carried out for 6 weeks simultaneously with the RT protocol. To assess patient compliance, all patients were provided with a diary to record every time they performed the mouthwash procedure. All patients were followed up biweekly.

Every two weeks, the patients were assessed for oral mucositis by the treating oncologist, which was also blinded, using the World Health Organization's (WHO) Oral Toxicity Scale to prevent bias. All grades of mucositis were assessed and recorded at the second, fourth, and sixth weeks of the RT. Each patient's body weight was recorded at the beginning and at the end of the treatment. The type of feeding by each patient was also documented.

RESULTS

We recruited 10 patients into the propolis group and 7 patients into the normal saline placebo group, for a total of 17 patients. No significant differences were noted in the baseline demographic characteristics, including race (p=0.60) and cancer staging (p=0.13), between the propolis and normal saline groups (Table I). The mean (SD) age of the patients was 47 (14.94) years in the propolis group and 47.29 (18.73) years in the normal saline mouthwash group (p=0.97). Most of the patients were Malay.

The distribution of the severities of mucositis was determined separately in the second, fourth, and sixth weeks of RT, based on the WHO Oral Toxicity Scale. The mean mucositis scores for the propolis vs. normal saline groups at the second, fourth, and sixth weeks of RT were 0.10 vs. 1.14, 0.50 vs. 2.00, and 1.20 vs. 2.86, respectively, and the differences between the two groups were statistically significant. The mean mucositis score for the normal saline group worsened throughout the assessment weeks, whereas the score for the propolis group improved.

The mucositis grading score over time also showed significant differences within each group (time effect). Table II shows significant differences in the mucositis grading for the propolis group between the second week and the sixth week (p=0.001) and between the fourth week and the sixth week (p=0.029). The normal saline group showed a significant difference in mucositis scores over time between the second week and the sixth week (p=0.009).

The mean difference in mucositis scores between the propolis and normal saline groups was 1.40 (1.02, 1.78), and this difference was statistically significant (p<0.001). Analysis of the mucositis grading scores based on the time–treatment interaction between the two groups revealed significant differences in all weeks (p=0.004, p<0.001, and p<0.001, for the second, fourth, and sixth weeks, respectively) (Table III).

Data analysis comparing the mean body weight pre and post RT within the propolis and normal saline groups, was made. The propolis group showed a mean weight difference of 8.0 (6.08, 9.92) kg pre and post treatment (p<0.001), while the normal saline group showed a mean weight difference of 11.87 (8.28, 15.47) kg pre- and post-treatment (p<0.001). The weight loss occurring between the pre and post treatments was statistically significant in both groups.

The mean weight difference between the propolis and normal saline groups was -2.564 (-17.05, 11.92), but this difference

Table I: Demographic characteristics of respondents (n = 17)

Variables	Group n (%)		p-value
	Propolis n=10	Normal saline n=7	
Age (years)	47(14.94)*	47.29(18.73)*	0.973[a]
Race			
Malay	7(70.0)	6(85.7)	0.603[b]
Chinese	3(30.0)	1(14.3)	
Staging			
2	2(2.0)	4(57.1)	0.127[b]
3	4(40.0)	0(0.0)	
4a	3(30.0)	3(42.9)	
4b	1(10)	0(0.0)	

*Mean (SD); aIndependent t-test; bFisher's exact test.

Table II: The comparison of mucositis grading scores within the propolis mouthwash and normal saline mouthwash groups over time (time effect)

Comparison	Propolis		Normal saline	
	Mean score different (95% CI)	p-value[a]	Mean score different (95% CI)	p-value[a]
Week 2 vs Week 4	-0.40(-0.88, -0.08)	0.110	-0.86(-1.72, 0.00)	0.050
Week 2 vs Week 6	-1.10(-1.63, -0.57)	0.001	-1.71(-2.90, -0.53)	0.009
Week 4 vs Week 6	-0.70(-1.33, -0.07)	0.029	-0.86(-1.72, 0.00)	0.050

[a] repeated measure ANOVA

Table III: Comparison of mucositis grading between the propolis mouthwash and normal saline mouthwash groups based on time (time–treatment interaction)

Time	Comparison	Mean difference (95% CI)	p-value
Week 2	Normal saline – Propolis	1.043 (0.39, 1.69)	0.004
Week 4	Normal saline – Propolis	1.50 (0.93, 2.08)	<0.001
Week 6	Normal saline - Propolis	1.657 (1.23, 2.08)	<0.001

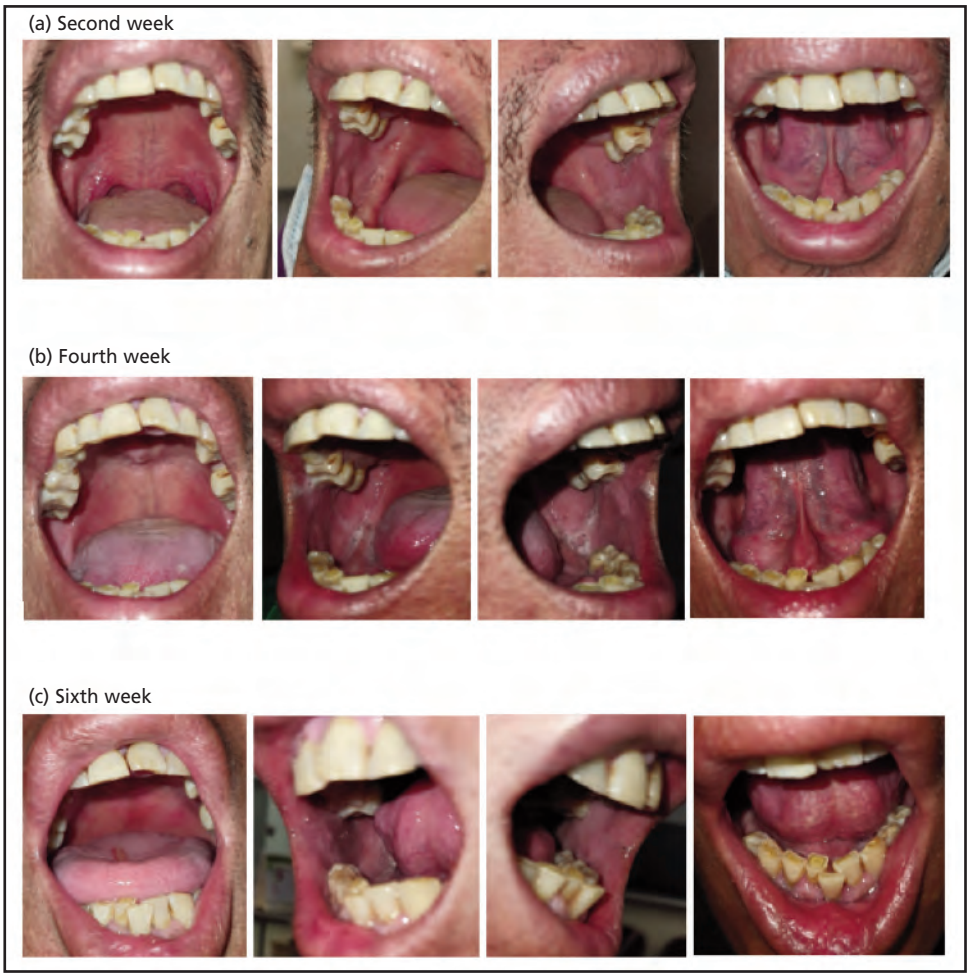

Fig. 1: Propolis mouthwash: Intraoral examination showed normal oral mucosa at the second and fourth weeks. Only a small tongue ulcer was seen at the sixth week (Grade 1: WHO Oral Toxicity Scale)

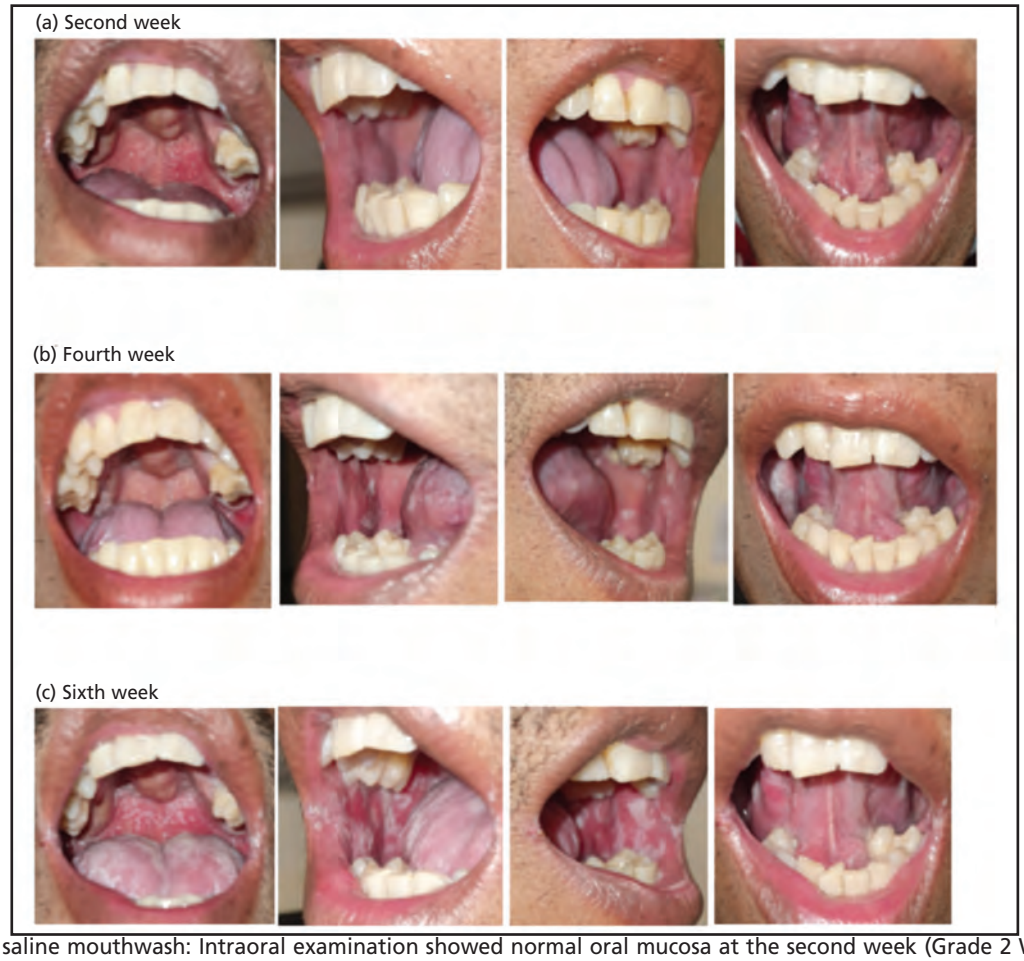

Fig. 2: Normal saline mouthwash: Intraoral examination showed normal oral mucosa at the second week (Grade 2 WHO Oral Toxicity Scale at the fourth week and Grade 3 WHO Oral Toxicity Scale at the sixth week)

was not statistically significant (p=0.711). Comparison of the body weight over time between the propolis and normal saline groups (time–treatment interaction) at week 2 and week 6 did not reveal statistically significant differences (p=0.930 and p=0.508, respectively).

The types of feeding between the propolis and normal saline groups were analysed using Fisher's exact test. All ten patients (100%) in the propolis group were able to take food orally, while six patients (85.7%) in the normal saline group required Ryles tube feeding, and only 1 (14.3%) was able to take food orally. The difference in type of feeding between the propolis and normal saline groups was statistically significant (p=0.001).

None of the patients who used the propolis mouthwash developed any adverse side effects.

DISCUSSION

Oral mucositis is an inflammation of the oral mucosa that leads to sores and ulcerative lesions in the oral cavity. It is especially seen in cancer patients undergoing combined RT and chemotherapy. Recent studies have determined that the mechanisms involved in the pathogenesis of mucositis are more complex than simply direct injury to the epithelium. RT-induced mucositis and chemotherapy-induced mucositis are believed to be identical in their mechanisms. The initiation of tissue injury by RT induces cellular damage, resulting in epithelial cell death. This process is then followed by upregulation of inflammation via activation of pro-inflammatory cytokines, and this upregulation can lead to further cell death and tissue injury. Inflammatory cell infiltration is also associated with mucosal inflammation and ulceration. Epithelial cell proliferation and restoration of the integrity of epithelium eventually occurs in the healing process.[3]

Oral mucositis can be very painful and can lead to significant malnutrition and weight loss due to poor oral intake. This can affect the quality of life and disrupt the cancer treatment protocol. The majority of head and neck cancer patients receiving RT are unable to eat by mouth due to mucositis pain, and they usually require nasogastric or gastrostomy tubes for feeding.[6]

At present, no specific treatment exists that can prevent RT-induced mucositis; therefore, most treatments focus on symptom relief. Mouth rinses using salt water are believed to be the simplest and most economical method to help in oral hygiene. Rinsing can swipe and remove oral debris while also maintaining moisture in the oral cavity. However, the overall effect is not ideal, and the patient still suffers from this debilitating complication.

Recently, many studies have attempted to identify the best way to minimise and prevent the complications of RT-induced mucositis. Some studies have focused on the use of natural bee products,[4] such as propolis, which is generally known as "bee glue" and is considered one of the most important bee products. Propolis contains numerous important organic compounds, vitamins, and minerals, and it shows antiseptic, anti-inflammatory, antibacterial, antioxidant, and anticancer properties. Its use has been approved based on numerous previous studies, making it very important and useful in treating various diseases. The healing properties of propolis are believed to arise due to the rich content of flavonoids, which are oxygen free radical scavenging compounds that can deactivate free radicals.[7] This deactivation helps to reduce the severity of oral mucositis and to hasten the healing process.

A meta-analysis study by Kuo et al.[8] on the efficacy of propolis mouthwash in cancer therapy-induced oral mucositis concluded that the severity of oral mucositis was significantly reduced by propolis mouthwash use (OR 0.35, p=0.003). However, in that meta-analysis, four studies involved patients who received chemotherapy only, and only one study administered RT. A study by Javadzadeh et al.[9] on the therapeutic effects of propolis in RT-induced mucositis in head and neck cancer patients examined 20 patients who were randomly given either propolis mouthwash or a placebo. All the patients were instructed to gargle and swallow 15 mL of the mouthwash three times a day for five weeks. A similar study led by Farzaneh et al.,[10] examined the efficacy and safety of propolis mouthwash in the management of RT-induced oral mucositis in 30 patients randomly assigned a propolis mouthwash or placebo; their patients were instructed to rinse their mouths with 20mL solution, three times a day, for four weeks. Both these studies used the National Cancer Institute Common Toxicity Criteria (NCI-CTC) to assess oral mucositis grading, and both reported that the propolis mouthwash was very effective at preventing RT-induced oral mucositis.

The present study is the first conducted in Malaysia to evaluate the effectiveness of propolis mouthwash in preventing RT-induced oral mucositis. It also differs from the previously mentioned studies in several ways. Our study focused on NPC patients, whereas the previous studies focused on patients with general head and neck cancers.[9,10] All 17 NPC patients in our study received CCRT, hence we excluded stage 1 NPC to standardise the treatment protocol, as in stage 1 NPC, they only received RT. Our patients were given propolis mouthwash (10 patients) or a normal saline placebo (7 patients), and all were instructed to rinse their mouths three times daily with 7mL solution for 60 seconds and then spit it out, for a duration of seven weeks, corresponding to the cancer treatment duration. The incidence of oral mucositis is usually observed after the first week of CCRT treatment; therefore, we started to assess the patients in the second week. For the assessment of oral mucositis, we used the WHO Oral Toxicity Scale rather than the NCI-CTC. In our study, we used a propolis mouthwash with a concentration of 2.5%, whereas the previous studies used propolis at 3%[9] and 80%.[10] However despite our use of a lower propolis concentration, by the end of the study, we saw a significant difference in the severity of oral mucositis between the two groups (Figures 1 and 2), as 8 of the 10 patients in the propolis mouthwash group had only grade 1 mucositis at the sixth week, and two patients had grade 2. By contrast, in the normal saline group, 6 of the 7 patients had grade 3 mucositis and only one patient had grade 2 mucositis. All the patients using propolis mouthwash were also able to take food orally by the end of the CCRT treatment, whereas all 6 patients with grade 3 mucositis in the normal saline mouthwash group required nasogastric tube feeding. Despite less severity of mucositis and the ability to take orally in the propolis group, there were no statistical differences in weight loss pre and post treatment in both groups. In terms of safety using the propolis mouthwash, none of the patients in the propolis group experienced any side effect or complication from using it. The other studies mentioned before also reported zero side effect or complication from the usage of propolis mouthwash. Hence, we confirmed that propolis mouthwash is safe for use by the patients.

CONCLUSION

We found that a 2.5% propolis mouthwash was effective at reducing the severity of oral mucositis, and its use was proven safe. None of the patients who used the propolis mouthwash developed any adverse side effects. In future, we encourage the health practitioners to provide propolis mouthwash as an adjunct treatment to reduce the severity of RT-induced oral mucositis for the NPC patients undergoing cancer treatment.

ACKNOWLEDGEMENTS

This research was supported by research grant from Malaysian Society of Otorhinolaryngology and Head Neck Surgeons (MSOHNS).

DECLARATION OF CONFLICT OF INTEREST

Authors declared no conflict of interest in this study.

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ORIGINAL ARTICLE

Palliative Prognostic Index as a predictor of mortality among geriatric patients with advanced chronic medical conditions

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ABSTRACT

Introduction: This study is to validate Palliative Prognostic Index (PPI) as a tool for six months prognostication in geriatric patients with advanced chronic medical conditions and to identify other independent prognostic markers of survival.

Methods: This was a prospective and observational study of 108 geriatric patients conducted at Pusat Jantung Hospital Umum Sarawak (PJHUS) Kota Samarahan and Sarawak General Hospital (SGH). The PPI scores were calculated and determined at the time of admission. Mortality is considered as the primary outcome. Sensitivity and specificity analysis were conducted to test the accuracy of PPI. The ideal cut-off value for PPI and other associated markers were determined based on the highest value of Youden Index. Cox regression analysis and survival analysis were applied to test the association between potential markers within six months.

Results: PPI score has a significant association with survival within six months based on univariate and multivariate analyses (p<0.05). Total PPI had a hazard ratio of 1.56 (95% Confidence Interval (95%CI): 1.33,1.57). The study shows PPI reported area under the curve-ROC of 0.945 with p<0.001. PPI score with cut-off value of six reports the highest accuracy in predicting death within six months with sensitivity and specificity of 88.6% and 90.6%, respectively. Total PPI score of >6 with serum albumin level ≤25, the sensitivity and specificity tested were 100.0%.

Conclusion: PPI has the potential to be a useful and significant predictor of mortality within six months in the geriatric population with an advanced chronic medical condition. This study also re-emphasised the strong prognostic role of other markers such as Palliative Performance Scale, Barthel Index, and serum albumin level. This study has identified that hypoalbuminemia cut-off value of 25g/dL analysed against PPI score of >5 revealed extremely high accuracy of prognostication for mortality.

KEYWORDS:
PPI, Geriatric, Palliative, Elderly, Prognostic, Albumin

INTRODUCTION

The average life expectancy at birth of the global population is projected to rise. In 2015, individuals aged ≥60 makeup of 12% of the global population or 901 million people, and this is projected to increase by 22% or 2.1 billion people by 2050.[1] In Malaysia, by 2020, the projection of the population aged ≥65 years could reach 7.1% of the population and the percentage could reach to 14.5% by 2040.[2] Advanced age is known to be one of the independent risk factors for higher mortality.[3-6] Various other studies have also shown that advanced chronic medical diseases are associated with a higher degree of mortality.

In dealing with patients who have poor prognosis, the commonest question being asked by patient and family members are; "How long have I got to live, Doctor?" The unfavourable outcome of the patient's prognosis, poorly trained staff, and difficulty to communicate with patients are among the challenges faced by physicians.[7] Indeed, discussion on this matter can be both intellectually and emotionally challenging. Studies have shown that physicians tend to be inaccurate and overestimate the prognoses of terminally ill patients which can have an impact on the patient's remaining quality of life and further delay admission to hospice or end-of-life care pathways.[8,9] The inaccuracy of projection of life will have a significant impact on the amount of unnecessary investigation and management of the patient which will further increase the financial burden on the health care system.[10]

The Palliative Prognostic Index (PPI), Palliative Prognostic Score (PaP), and Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS) are among the many prognostic models that have been developed and validated for patients with cancer. Nevertheless, the challenges in predicting the prognoses in advanced chronic medical condition and non-cancer patients remain difficult due to heterogeneity of non-cancer patients and unpredictable course of the disease. Furthermore, the usefulness and reliability of the prognostic models in estimating the survival of <6 months in non-oncological patients have shown poor discriminative power and remain uncertain.[11] However, a study by Nieto et al., has shown that PPI can be a useful tool

This article was accepted: 26 May 2022
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in predicting 6-month survival of patients with advanced medical conditions.[4]

Herein, this study aims to investigate the role of PPI score as a prognostic tool in the geriatric patients with advanced chronic medical conditions. It was crucial to exclude patients with known diagnosis of cancer in the study as the PPI score has been previously validated.[9,12,13] PPI comprises of assessment of Palliative Performance Scale (PPS), oral intake, presence of oedema, dyspnoea at rest and delirium. In the earlier study by Morita et al.[14], the authors reported that PPI scores of >6 had three weeks survival prediction with sensitivity of 80% and specificity of 85% based on the survival of 150 terminally ill cancer patients. Based on that study, patients were classified into three groups, Group A (PPI Score 0.0-4.0), Group B (PPI Score 4.1-6.0), and Group C (PPI Score 6.1-15.0). The PPI score then can be used to predict survival for patients with short survivals (<3 weeks or between 3 and 6 weeks) but an estimation of long-term survival (>6 weeks) in advanced cancer patients is limited.

Several other tools and biological markers have been developed and investigated as prognostic markers. Within the scope of this study, the value of PPS, Barthel Index (BI), and serum albumin level as a prognostic marker of survival will also be investigated. The PPI score uses the PPS, which is a modification of the Karnofsky Performance Scale.[15] The PPS criteria include the extent of disease affecting the level of activities, ambulatory status, level of self-care, oral intake status, and level of consciousness. PPS has been shown to be a reliable prognostic tool and correlates well with median survival time in cancer patients.[15,16] The widely used BI, an ordinal scale to measure the functional level of independence, has also been shown to be associated with the risk of mortality in geriatric patients.[17] Furthermore, many studies have described biological parameters such as albumin as an important biomarker for prognosis.[18,19]

General objectives

To validate PPI as a tool for prognostication in geriatric patients with advanced chronic medical conditions.

Secondary objectives

To validate other independent prognostic markers of survival (PPS, BI, and serum albumin level) in the geriatric patients with advanced chronic medical conditions.

METHODOLOGY

Overview of research design

This study was a prospective and observational study conducted at a 16-bedded Geriatric Unit in Pusat Jantung Hospital Umum Sarawak (PJHUS) Kota Samarahan and the general medical wards at Sarawak General Hospital (SGH). Majority of the geriatric age-group patients would be admitted in SGH for initial assessment and treatment prior to transferal to Geriatric Unit for continuity of care and rehabilitation process. The study period was from early September 2018 till end of October 2019. Participation in this study was strictly voluntary and written informed consent was obtained from the patients or the next of kin. Demographic, epidemiological, and clinical data at the time of enrolment into the study were collected. The PPI scores were calculated and determined at the time of admission based on the sum of PPS, assessment of oral intake obtained directly from the patient or the next of kin, presence of oedema, and delirium. The PPS, BI, and serum albumin were identified on admission. The participants were followed-up throughout their admission in the hospital and mortality is considered as the primary outcome. Patients discharged from the ward had follow-up telephone calls for a total duration of six months from the enrolment into the study.

This study was approved by Malaysian Research Ethics Committee, Ministry of Health Malaysia (research ID NMRR-17-2923-38888).

Inclusion and exclusion criteria

The inpatients selected were above the age of 60 and had been diagnosed with one or more of the advanced chronic medical conditions such as cardiac failure with basal New York Heart Association Functional Class 3-4, respiratory disease with basal dyspnoea of Medical Research Council Class ≥3 or on chronic home oxygen therapy, stage 4-5 chronic renal failure based on KDOQI classification, chronic liver disease with Child-Pugh Score ≥7 and all neurological disease with established cognitive impairment of MMSE ≤30 or established limitation with BI <60 points. The exclusion criteria from this study were the presence of active neoplasm and had previously enrolled in the study.

Sample size determination

The aim of this study was to measure the accuracy of PPI as a predictor of mortality among geriatric patients with advanced chronic medical conditions. Hence, the sample size formula was based on sensitivity and specificity analysis. When the prevalence of mortality is expected at 30%, a minimum sample size of 163 subjects (including minimum 49 subjects died) will be required to achieve a minimum power of 80% (actual power=81.0%) for detecting a change in the percentage value of sensitivity of a screening test from 0.50 to 0.70, based on a target significance level of 0.05 (actual p=0.044).[20]

Statistical method

Descriptive analysis was conducted to present the characteristics of patients and medical conditions. Meanwhile, sensitivity and specificity analysis were conducted to test the accuracy of PPI and other markers in predicting survival and mortality. The ideal cut-off was determined based on the highest value of Youden Index for all the markers. Cox regression analysis and survival analysis were applied to test the association between potential markers and survival between six months. All analyses were conducted using SPSS software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc) and diagnostic calculator (2020 MedCalc Software Ltd)

RESULTS

A total of 108 patients were enrolled in this study, 58.3% were male and 41.7% female with a mean age of 72.81 (±8.024). The intended minimum sample size of 163 subjects was not achieved as the study had poor participation due to the

Table I: Demographic and Baseline Characteristic of Participants

		Mean (SD)	n (%)
Age (years)		72.81 (8.024)	
Gender	Male		63 (58.3)
	Female		45 (41.7)
BMI (kg/m^2)		23.14 (4.7)	
fulfil inclusion Criteria	Neurological disease		42 (38.9)
	Respiratory disease		37 (34.3)
	Renal failure		37 (34.3)
	Cardiac failure		14 (13)
	Chronic liver disease		2 (1.9)
Co-morbidity	Hypertension		77 (71.3)
	Anaemia		57 (52.8)
	Diabetes mellitus		49 (45.4)
	Chronic kidney disease		42 (38.9)
	Stroke		33 (30.6)
	COPD		31 (28.7)
	Dyslipidaemia		24 (22.2)
	Ischaemic heart disease		18 (16.7)
	Cardiac failure		17 (15.7)
	Bronchiectasis		13 (12)
	Atrial fibrillation		11 (10.2)
	Pressure ulcer		11 (10.2)
	Pulmonary tuberculosis		7 (6.5)
	Venous thromboembolism		7 (6.5)
	Asthma		4 (3.7)

Note: BMI, Body Mass Index

Table II: Hazard Ratio (95% Confidence Interval) for Potential Markers and Survival Within Six Months

Markers	Crude			Adjusted[a]		
	HR	95%CI	p-value	HR	95%CI	p-value
Total PPI	1.444	1.327, 1.571	<0.001	1.559	1.402, 1.734	<0.001
Palliative Performance Scale	2.519	1.921, 3.304	<0.001	2.975	2.188, 4.045	<0.001
Albumin	0.945	0.909, 0.982	0.004	0.940	0.896, 0.986	0.011
Barthel Index	5.217	2.749, 9.900	<0.001	6.017	2.836, 12.768	<0.001

[a]Statistics were calculated using multivariate analysis to control for gender, age, and diagnosis in the analysis.
Note: PPI, Palliative Prognostic Index

Table III: Area under curve-ROC for Potential Markers and the Accuracy to Predict Survival Within Six Months and Mortality

Markers	AUC	95% CI		Cut-off	Sensitivity	Specificity
Predict survived						
Barthel Index	0.772	0.678	0.866	60	0.859	0.682
Albumin levels	0.665	0.561	0.769	29.5	0.803	0.455
Palliative Performance Scale	0.861	0.787	0.934	50	0.886	0.766
Predict died						
PPI	0.945	0.904	0.985	6	0.886	0.906

Note:
All results were statistically significant, p<0.05

Table IV: Accuracy of Palliative Prognostic Index (PPI) on Selected Cut-off of Albumin

Albumin	PPI	Diagnostic accuracy	Value (95%, CI)
ALL	>5	Sensitivity	88.6% (75.4%, 96.2%)
		Specificity	90.2% (79.8%, 96.3%)
		PPV	86.7% (75.1%, 93.3%)
		NPV	91.7% (82.8%, 96.2%)
≤25 g/dL	>5	Sensitivity	100.0% (69.2%, 100.0%)
		Specificity	100.0% (47.8%, 100.0%)
		PPV	100.0%
		NPV	100.0%

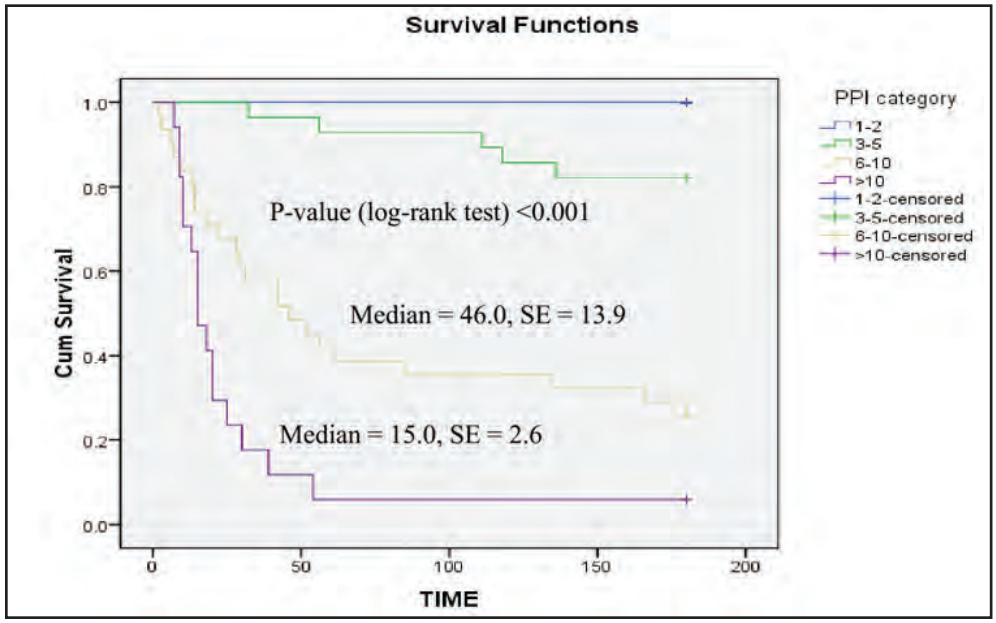

Fig. 1: Palliative Prognostic Index (PPI) categories and magnitude of survival

sensitive nature of the study that dealt with the trajectory of life. Moreover, in this study, a total of nine patients were excluded as they did not fulfil the inclusion criteria and had loss of follow-up upon discharge. Table I shows the demographic and baseline characteristic of the participants. In this study, the most frequent inclusion criteria were neurological disease (42 patients, 38.9%), followed by respiratory disease (37 patients, 34.3%), renal failure (37 patients, 34.3%), cardiac failure (14 patients, 13%), and chronic liver disease (two patients, 1.9%). The predominant neurological disease encountered in this study was mainly stroke. There were 24 patients included in this study that had more than one inclusion criteria fulfilled.

PPI score and the other three markers (PPS, BI, and serum albumin level) were selected and tested to determine their association with survival within 6 months. In Table II, this study has identified that all four markers have an association with survival within 6 months based on univariate and multivariate analyses ($p<0.05$). Total PPI, PPS, and albumin had hazard ratio of 1.56 (95% Confidence Interval (95%CI): 1.33, 1.57), 2.98 (95%CI: 2.19, 4.05), and 0.94 (95%CI: 0.90, 0.99), respectively. BI has the highest hazard ratio of 6.02 (95%CI 2.84, 12.77) in multivariate analysis. As expected, albumin had reversed association with survival within six months (Table II). In this study, the accuracy of potential markers was assessed using Receiver Operating Characteristics (ROC) analysis to determine the optimal cut-off based on Youden Index. The study shows PPI reported area under curve-ROC of 0.945 with p-value of <0.001. PPI has the highest accuracy followed by PPS, BI, albumin and the optimal cut-off is presented in Table III. PPI and other markers have the potential to predict the status of survival (survived or died) within six months.

PPI is initially intended to be used to predict survival in terminally ill cancer patients for a period of <6 weeks but here the authors have identified that PPI with cut-off value of six reports the highest accuracy to predict death within six months with sensitivity and specificity of 88.6% and 90.6%, respectively (Table III). Other markers such as BI has a cut-off of 60 (sensitivity 85.9%, specificity 68.2%) and serum albumin cut-off value at 29.50 (sensitivity 80.3% and specificity 45.5%) to predict survival. In this study, PPS cut-off value 50 has the ability to predict survival with sensitivity and specificity of 88.6% and 76.6%, respectively.

The PPI scores were further categorised into four groups (PPI Score 1-2, 3-5, 6-10, and >10). In Figure 1, the selected categories show a significant difference in the magnitude of survival and good discriminatory power, whereby PPI score >5 can be considered as higher risk of mortality compared with the lower PPI score categories (Categories 1-2 and 3-4). Further analysis was carried out to assess the accuracy of PPI in predicting survival within six months based on selected cut-off for albumin. When the PPI is >5 and albumin ≤25, the sensitivity and specificity were 100.0% (Table IV). For PPI score >5 irrespective of the value of albumin, the sensitivity and specificity remain high at 88.6% (95%CI: 75.4%, 96.2%) and 90.2% (95%CI: 79.8%, 96.3%), respectively.

DISCUSSION

This study shows that PPI taken on admission is a useful, significant, and can potentially be an important tool to predict mortality within six months period. PPI had been numerously validated as a predictive model for mortality in patient with underlying cancer.[9,12,13] Nevertheless, studies which look into PPI as a prognostic tool in non-cancer patients are limited. In Table II, the total PPI score has a

hazard ratio of 1.559 (p<0.001) and Table IV indicates that PPI score of >5 had a good sensitivity (88.6%) and specificity (90.6%). Morita et al., initially reported that prediction of 3-week survival in terminally ill cancer patients was made with a sensitivity of 80% and specificity of 85% using PPI cut-off value >6.[14] Further analysis using Kaplan-Meier plot indicates that PPI strongly correlates with mortality risk as can be seen in Figure 1 which shows the categories with the PPI score of 6-10 and >10 are associated with median mortality of 46 days and 15 days, respectively. Therefore, PPI assessment is a useful screening tool to predict mortality among the geriatric patients with advanced chronic medical conditions. A multicentre prospective and observational study done by Nieto et al also concluded that PPI can be a useful tool in predicting 6-month survival of patients with advanced medical conditions.[4]

Anderson and Downing had introduced PPS, which was later incorporated in PPI and had been shown to be a very important clinical assessment in palliative care and predictor of survivor.[15] The reliability and validity of PPS are proven in a clinical performance assessment tool for palliative care patient.[16] This study has shown that PPS cut-off score of 50 has a sensitivity of 88.6% and specificity of 76.6% to predict survival within the 6-month study period (Table III). This cut-off value of 50 reflects the overall functional performance of patient in ambulation, level of activity, self-care, oral intake, and their level of consciousness.

Matzen et al., reported that BI is a strong independent predictor of survival in older patients who were admitted to the acute geriatric unit.[21] The hazard ratio of BI for survival within 6 months in the study was 6.017 (p<0.001) and based on Table III, the cut-off value for BI was 60, having 85.9% sensitivity and 68.8% specificity. In a Danish nationwide population-based cohort study, it was also evident that BI at admission was strongly and independently associated with mortality in geriatric patients.[17] Similar pattern can be seen in the study when analysing both BI and PPS as predictors of six months mortality among the geriatric patients with advanced chronic medical conditions.

This study reinforces the importance of serum albumin level as an independent prognostic marker of survival using multivariate analysis with a hazard ratio of 0.940 (p=0.011). Albumin cut-off value was 29.5 for prediction of 6-month survival with 80.3% sensitivity and 45.5% specificity. Serum albumin level is associated with 30-day all-cause mortality in acutely admitted medical patient and has an acceptable discriminatory power and good calibration.[22] In a meta-analysis conducted on 90 cohort studies with 291,433 patients by Vincent et al., revealed that for each 10g/L decline in the serum albumin concentration could significantly increase the odds of mortality by 137% and morbidity by 89%, prolonged intensive care unit and hospital stay by 28% and 71%, respectively.[22]

Moreover, the authors have identified that serum albumin level of <25 g/dL with a PPI score of >5, the sensitivity, specificity, positive predictive value, and negative predictive values have shown a diagnostic accuracy of 100%. No other studies at the time of this research had looked into the relation of hypoalbuminemia with a high PPI index as a tool to prognosticate patient survival in both cancer and non-cancerous condition. Whether incorporation of serum albumin level with the PPI score could potentially be a better prognostication tool is yet to be explored. Knowing that low serum albumin could potentially be reversible, could intervention potentially reduce the risk of mortality especially in the setting of high PPI?

LIMITATION

The study sample size did not achieve the desired planned sample size (n=163 subjects) due to the sensitive nature of the study that dealt with trajectory of life. Initially, the sample size planning was calculated based on a prevalence of 30.0% and to detect a change in sensitivity from 0.50 to 0.70. Since this study had achieved more than 80% sensitivity and therefore the sample size of 108 is sufficient to get significant results. The authors have recalculated the sample size to detect a change of sensitivity from 0.50 to 0.80 based on a prevalence of 30%. The study only requires a minimum sample size of 67 subjects with at least 20 mortalities.[20]

CONCLUSION

This study indicates that PPI taken on admission has the potential to be a useful and significant predictor of mortality within six months in the geriatric population with an advanced chronic medical condition. Furthermore, this study emphasised the strong prognostic role of functional status such as PPS, BI and hypoalbuminemia. All these findings could prove to be a useful adjunct in clinical decision making and discussion with patients' family in determining the trajectory of a patient condition. Based on the sample of the study population, the authors have identified that hypoalbuminemia cut-off value of 25 g/dL analysed against PPI score of >5 revealed extreme high accuracy of prognostication for survival. More research is needed to verify this association between low albumin and high PPI score in the future.

ACKNOWLEDGEMENTS

The authors would like to thank the Department of Geriatrics, Sarawak Heart Centre, Sarawak General Hospital, and University Malaysia Sarawak (UNIMAS) for their institutional support throughout the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This study was approved by Malaysian Research Ethics Committee, Ministry of Health Malaysia (research ID NMRR-17-2923-38888 (IIR).

FUNDING

This research was funded by the Small Grant Scheme of the Research, Innovation, and Enterprise Centre. Universiti Malaysia Sarawak (Project ID: F05/SGS/1816/2019)

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ORIGINAL ARTICLE

Incidence and determinants of catastrophic health expenditure among low-income Malaysian households

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ABSTRACT

Introduction: Catastrophic health expenditure (CHE) incurs when out-of-pocket health expenditure (OOPHE) exceeds a certain threshold, therefore exposing households to financial hardship, with the low-income population being most vulnerable. Data related to the incidence and determinants of CHE among the low-income population in Malaysia are lacking. This study aims to determine the incidence and determinants of CHE among Malaysian low-income households.

Methodology: This is a cross-sectional study using data from 6,720 low-income households from the national Household Expenditure Survey (HES) 2016 conducted from May 2016 till February 2017. The data were analysed using IBM SPSS software 25.0. OOPHE in this study included all spending on healthcare products and services by the household. CHE was identified in households with OOPHE of at least 10% of total monthly income.

Results: The incidence of CHE at the threshold of 10% household income was 1.7% (n=112). The determinants of CHE were households with any accident or medical insurance (p<0.001), having less than five members in a household (p<0.001), presence of elderly (p=0.024), and hospitalisation (p=0.021). In contrast, employment of the head of household (p=0.003) and having a child aged ≤5 years old (p=0.033) protect households from CHE.

Conclusion: In the context of this study, the incidence of CHE among the low-income Malaysian population was low, indicating that a majority of the low-income population is protected from financial catastrophe. Regardless, the determinants of CHE among low-income population should be considered in future health policies.

KEYWORDS:
Out-of-pocket health expenditure, catastrophic health expenditure, Malaysia, low-income household

INTRODUCTION

Out-of-pocket health expenditure (OOPHE) describes any out-of-pocket payment to receive any form of health services and is considered the most regressive and inequitable way to fund the health system.[1] Once a household reached a certain threshold of OOPHE, they were considered as experiencing catastrophic health expenditure (CHE).[2] The sustainable development goal (SDG) 3.8.2 has adopted the threshold of CHE at 10% or 25% of income or consumption.[2] CHE is a barrier to attain universal healthcare as everyone should be granted access to healthcare based on what they need and not based on what they can pay for.[2] Unfortunately, CHE has negative consequences on the household economy, health, and overall quality of life. Households experience various negative consequences from CHE, for example, depletion of their savings,[3] failure to make household payments,[4] incurring debt[3] as well as selling valuable assets.[5] Additionally, due to fear of health expenditure, some people refrain from seeking needed health services and instead seek healthcare from unqualified healthcare providers6 with subsequent lower quality of life.[7] Worse still, although CHE can affect anyone, those with low income and burdened with high living costs are the most vulnerable.[8-10]

The healthcare services in Malaysia are provided via a mix of public and private delivery system. Public health care in Malaysia, which is delivered mainly through the Ministry of Health (MOH)-owned facilities is funded predominantly from general taxation.[11] Private health care is largely delivered through for-profit hospitals and clinics and is funded by a mixture of OOPHE, private health insurance, and employer-sponsored care.[11] Unfortunately, the Malaysia National Health Account had demonstrated that throughout the 2009-2016 annual time series, the share of OOPHE to total health expenditure in Malaysia showed a consistent increase from 29% (2009) to 38% (2016).[11] For the Malaysian poorest income quintile, the mean annual per capita OOPHE was RM 279 (USD 92.8) in the year 2011.[12] Unfortunately, despite documenting lower mean per capita OOPHE of RM238 (USD 64.98) in the year 2015, the OOPHE of the Malaysian households in the poorest income quintile were higher than the other quintiles (except for the richest quintiles).[13] The World Health Organization (WHO) estimated that the CHE incidence among the low-income population in Malaysia is at 0.1%.[14] However, this estimate was based on data more than 10 years ago.

Previous literature had established several factors associated with CHE, in particular socio-demographic factors like age,[15,16] gender,[17] education level,[18,19] and employment.[19,20] Other factors include the presence of chronic disease or disability[21,22] or healthcare utilisation[23] and household factors like household size[24,25], presence of elderly[21,22] and having children.[21,26] Within the Malaysian context, the factors contributing towards CHE among the elderly are cancer, being male and Malay ethnicity[27] while among cancer patients, those from low-income households and seek treatment at private health facilities were associated with CHE.[4] Nevertheless, the determinants of CHE among the

This article was accepted: 31 May 2022
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Malaysian low-income population are largely unknown. Therefore, with the intention to fill the data gap, our study had two objectives: first, to investigate the CHE incidence among low-income Malaysian households and second, to identify the determinants towards CHE among the low-income Malaysian households.

MATERIALS AND METHODS

This is a cross-sectional study.

Data source

This study utilised the available data from the Household Expenditure Survey (HES) 2016 conducted by the Department of Statistics Malaysia (DOSM) which was obtained with permission from the Universiti Putra Malaysia (UPM) Sultan Abdul Samad Library Databank. The HES 2016 was a survey organised by the Department of Statistics Malaysia (DOSM) from May 2016 till February 2017, conducted in all states in Peninsular Malaysia, Sabah, and Sarawak, including urban and rural areas with a selection of households living in private living quarters based on a two-stage stratified sampling approach.[28] However, the survey excluded certain remote and aboriginal ('Orang Asli) settlement and those living in residential institutions such as hostels, elderly homes, and welfare homes.[28] Trained interviewers visited selected households to obtain information on demography, income, and the household expenditure using a set of questionnaires based on the Classification of Individual Consumption According to Purpose (COICOP) published by the United Nations Statistics Division (UNSD).[28] The HES 2016 survey yielded data for a total of 48,491 households,[28] in which random data for around 14,000 households were shared with the UPM Sultan Abdul Samad Library.

Participant

The sample population is the low-income households selected in the HES 2016. We applied the hypothesis testing method with calculated sample size of 6,052 based on a previous study,[26] hence we applied universal sampling. We included households with a total monthly income of less than RM4,360.00, which represent households at the bottom 40% of the household income tier in the year 2016.[29]

Components of OOPHE

The OOPHE included in the HES 2016 were categorised into four classifications; medicine and health products (e.g., medications, consumables and medical equipment), outpatient care, inpatient health services, and payments for any accident or medical insurance. The recall periods for medicinal products and accident or medical insurance were 1 month while expenditure for outpatient services, inpatient treatment, and health equipment were set at 1 year.

Data analysis and outcome

The outcome in this study was CHE, which was estimated based on the 'budget share' approach. Using this approach, we calculated the average total monthly OOPHE for each household and divided them with the monthly household income to obtain the proportion of monthly OOPHE expenditure for the respective household relative to their monthly household income. Households with the proportion of OOPHE of at least 10% of monthly total household income were considered as experiencing CHE.[2] The independent variables were selected based on published studies. Data analysis was conducted using the IBM SPSS 25.0. Descriptive analysis was used to describe the household characteristics and prevalence of CHE. Subsequently, single and multiple logistic regression were conducted to identify the determinants of CHE.

Ethics

We obtained ethical permission from the Universiti Putra Malaysia Ethical Committee for Research Involving Human Subject (JKEUPM) (Reference Number : JKEUPM-2020-061).

RESULTS

A total of 6,720 households were included in our study. Descriptive analysis demonstrated that Sarawak (n=1181) and Sabah (n=1118) contributed to the highest number of low-income households. The majority of the head of households (HHH) were mostly male (79.8%), married (72.3%), and employed (90.3%). The distribution and socio-demographic characteristics of households are presented in Table I.

Our findings noted that a significant portion of households (88%) reported having any amount of OOPHE. The incidence of CHE at the threshold of 10% of total monthly household income among the low-income households was 1.7% (n=112). Analysis of OOPHE pattern revealed that more than half (56.9%) of households reported expenditure for medicine and health products while two-third of households (71.6%) reported expenditure to obtain outpatient healthcare services. Unfortunately, only a minority of the households (3.9%) reported expenditure for some accident or medical insurance. Table II gives the summary of characteristics of OOPHE.

The single logistics regression analysis demonstrated that 11 variables were significantly associated with CHE; namely sex of head of household (HHH), age of HHH, marital status of HHH, HHH employment status, household size, presence of elderly in a household, presence of female, presence of children 5 years old and less, household income, presence of accident or medical insurance and presence of hospitalisation in a household. These variables were then included in the preliminary models for multiple logistic regression. For the final model, the forward LR method was applied. The Hosmer–Lemeshow test accepted the goodness-of-fit hypothesis (χ^2=7.332, df=7, P=0.395). The model made the correct classifications 98.1% of the time. However, the model only explained 10.9% (Neglekerke R2) of variance in the CHE status. No multicollinearity or interaction between variables was found. The receiver operating characteristics (ROC) curve showed area under the curve of 0.783 (p<0.001), hence the model had fairly good predictive power.

The final model revealed that six variables predict the probability of CHE among low-income households; in particular employment status of head of household (HHH), household size, presence of elderly in a household, having children aged 5 years old or less, enrolment in accident and

Table I: Household Distribution and Characteristics (N=6702)

Characteristics	Frequency	Percentage
State		
Sarawak	1181	17.6
Sabah	1118	16.6
Kelantan	646	9.6
Perak	574	8.5
Kedah	551	8.2
Johor	469	7.0
Pahang	424	6.3
Selangor	364	5.4
Terengganu	304	4.5
Pulau Pinang	302	4.5
Negeri Sembilan	249	3.7
Melaka	171	2.5
Perlis	163	2.4
WP Kuala Lumpur	139	2.1
WP Labuan	57	0.8
WP Putrajaya	8	0.1
Strata		
Urban	3716	55.3
Rural	3004	44.7
Gender*		
Male	5361	79.8
Female	1359	20.2
Age*		
< 60 years old	5105	76
≥60 years old	1615	24
Marital status*		
Single/widowed/divorced	1861	27.7
Married	4859	72.3
Education level*		
No/informal	546	8.1
Primary	1685	25.1
Secondary	3981	59.2
Tertiary & above	508	7.6
Employment*		
Unemployed	275	4.1
Employed	6086	90.6
Retired	359	5.3
Household size		
≤ 4 members	4594	68.4
≥ 5 members	2126	31.6

WP = Wilayah Persekutuan, *referring to head of household (HHH)

Table II: Characteristics of Out-of-pocket Health Expenditure (OOPHE)(N=6720)

Characteristics	Frequency (n)	Percentage (%)
Household having any amount of OOPHE		
No	756	11.1
Yes	5964	88.9
Household experiencing CHE		
No	6,608	98.3
Yes	112	1.7
Type of health expenditure		
Medicine and health products		
No	2894	43.1
Yes	3826	56.9
Outpatient health services		
No	1975	29.4
Yes	4745	71.6
Inpatient health services		
No	6526	97.1
Yes	194	2.9
Medical or accident insurance		
No	6457	96.1
Yes	263	3.9

Note: CHE, catastrophic health expenditure

Table III: Logistic Rgression Analysis for Predictors of Catastrophic Health Expenditure Among Low-income Households

Variable	Single logistics regression				Multiple logistics regression			
	COR	95% CI for COR		p-value	AOR	95% CI for AOR		p-value
		Lower	Upper			Lower	Upper	
Sex of HHH								
Male	1							
Female	1.547	1.022	2.343	0.039				
Age of HHH								
Age <60 years old	1							
Age ≥60 years old	3.874	2.656	5.649	<0.001				
Marital status of HHH								
Single/widow	1							
Married	0.472	0.324	0.688	<0.001				
Employment status of HHH								
Unemployed	1				1			
Employed	0.285	0.157	0.518	<0.001	0.385	0.206	0.720	0.003
Household size								
≤4 members	4.265	2.283	7.965	<0.001	2.025	1.028	3.987	0.041
≥5 members	1				1			
Presence of elderly								
No	1				1			
Yes	3.7	2.48	5.52	<0.001	1.918	1.091	3.372	0.024
Presence of female								
No	1							
Yes	0.482	0.281	0.825	0.008				
Having child ≤5-year-old								
No	1				1			
Yes	0.163	0.071	0.371	<0.001	0.383	0.158	0.927	0.033
Household income								
Q1 (poorest)	1							
Q2	0.78	0.287	0.804	0.005				
Q3	0.474	0.283	0.794	0.005				
Q4	0.495	0.298	0.823	0.007				
Having accident/medical insurance								
No	1				1			
Yes	3.494	1.999	6.108	<0.001	4.076	2.288	7.260	<0.001
Hospitalisation								
No	1				1			
Yes	2.343	1.125	4.881	0.023	2.426	1.143	5.149	0.021

COR: crude odds ratio, AOR: adjusted odds ratio, CI: confidence interval, Bold = p-value significant at <0.05
Note: HHH, Head of Households,

medical insurance as well as the presence of hospitalization in a household. Table III presented our regression analysis showing the determinants of CHE among the low-income Malaysian households.

DISCUSSION

Incidence of CHE

In the context of our study where OOPHE data included all expenditure on healthcare products and services by the households, the results demonstrated that the incidence of CHE among low-income households in Malaysia (1.7%) is lower than the CHE estimate for the general Malaysian population at 4.6%30 or other specific Malaysian populations, in particular, the elderly at 2%[27] and cancer patients at 51%.[4] This proportion is also lower than reported by another study involving low-income population in Thailand (10.3%), Indonesia (19.3%), Delhi (42.1%), and Bhubaneswar (18.3%) in India.[6] Therefore, it is evident that the current available healthcare system appears to be able to protect the larger part of the low-income Malaysian population from financial catastrophe. Nevertheless, despite the small proportion of CHE demonstrated from our study, as these households represented 2.7 million low-income Malaysian households,[29] this proportion reflects more than 46,000 low-income households at risk of experiencing CHE in Malaysia. Hence, identifying these vulnerable population and carrying out appropriate interventions could improve the financial protection among the low-income Malaysian households. Despite the low incidence of CHE found among the study population, the incidence of CHE in our study might be an underestimated value for several reasons. First, the 'budget share' approach has no consideration of actual household consumption for basic necessities like food and shelter. In reality, low-income households may spend a sizable portion of their income on food and other basic needs, hence their remaining income which represents the actual ability to pay for healthcare is much lower. Therefore, using the 'budget share' approach may underestimate the incidence of CHE among poor households. Secondly, long recall periods and having proxy respondents to recall health events for the whole household may cause underreporting of health expenditure.

Determinants of catastrophic health expenditure

Our results revealed that only 3.9% of households reported some form of accident or medical insurance, implying that insurance does not play many roles in healthcare financing among the low-income Malaysian households. Enrolment in medical insurance is expected to protect households from experiencing CHE. In line with this, previous studies had demonstrated higher CHE among households which did not have any form of medical insurance.[31-33] Interestingly, our study demonstrated that a household which reported any accident or medical insurance has 4.0 times higher odds of incurring CHE as compared to non-insured households. Supporting our finding, a study in Thailand demonstrated that households which register with their government civil servant insurance scheme were significantly associated with CHE.[34] Several theories have been proposed to explain why insurance enrolment is linked with CHE. To begin with, certain insurance may have limited coverage, with specific hospital services such as drugs, beds, and procedures being excluded from the policy.[34] Furthermore, insurance plans may not cover outpatient charges, rehabilitation, or long-term care, leaving households to pay for these treatments out-of-pocket.9 Secondly, enrolment in insurance scheme subject patients and health providers for moral hazard, indicated by induced demand; albeit unnecessary medical services for patients.[9,35] Third, there is a possibility of adverse selection in the commercial insurance market. As insurance participation and its premium are based on voluntary choice, the high-risk people are more inclined to buy medical insurance.[1] These people are those with existing disease which definitely needs healthcare services, therefore they are also at risk for CHE.[1] The mechanism of CHE among the low-income households reported having insurance in Malaysia is beyond the scope of this study; hence, we recommend further research into this issue in order to be able to plan for an equitable, inclusive, and affordable insurance for the low-income population in Malaysia.

Our study found that hospitalisation among any household members increases the odds of CHE by 2.4 folds, most likely due to direct medical expenses related to admission to hospital, as supported by other studies from India[36] and Iran.[37] In fact, duration of hospitalization and admission to tertiary hospital further increased the risk for CHE.[38] In addition, indirect medical costs like transportation costs to visit the sick and indirect costs involving loss of income for the patients or their carer due to hospital admission may aggravate the already limited financial resources for low-income households.

Previous study argued that larger household size render more household members at risk for needing healthcare,[15] therefore these households were more likely to slip into CHE. Interestingly, our study found that households with four or less members are associated with CHE as compared to households with five or more members. Although our study is unable to provide any explanations related to these findings, previous studies suggested that having more household members provide a better ability to care for other family members, hence reducing the need to seek health service[21] and more household members that contribute towards household income, hence the pooling of income protect households from CHE.[39] Therefore, it is possible that households with less members have less ability to provide care for other members, resulting into higher demand for healthcare services. Additionally, they may have a reduced ability to generate household income, increasing the risk of CHE.

Our study demonstrated that the presence of elderly in a household increased the odds of incurring CHE by 1.9 folds, which was not surprising considering the elderly are associated with a higher prevalence of chronic diseases like diabetes, hypertension, and cancer as demonstrated by other studies.[20,40] As a result, there is increased demand for healthcare services from either conventional or alternative care providers among the elderly, likely resulting into a subsequent increase in OOPHE.

Finally, we found that employment of head of household and the presence of children aged 5 years old and less were protective factors from CHE. Supporting these findings, studies in other countries had demonstrated the association between unemployment and CHE.[9,33] As the results also show that households belonging in the better income quartile (Q2, Q3 and Q4) have lower risk for CHE, these findings highlighted that better household economic conditions increase the protection from CHE. Interestingly, our findings pointed out that the presence of children aged ≤5 years old protected households from CHE. Another study demonstrated a similar finding, thus argued that younger children were associated with younger parents which are expected to be healthy with a lower need of healthcare services for the household.[26] Additionally, it is possible that the free-of-charge preventive and curative primary care services for children in Malaysia have contributed to financial protection among households with younger children.

We believe that this study has provided useful insight into the financial protection among low-income Malaysia household using a nationwide survey data. Regardless, our study has several limitations. First, the cross-sectional study design only allows for demonstration of the association among variables with CHE. However, further study will provide more understanding on the pathways towards CHE. Secondly, recall bias may result into underestimation of household health expenditure. Third, certain aboriginal household and population in institutions like old folk's homes were excluded from the study. Finally, some possible factors contributing towards CHE were not investigated, for example, having chronic disease, disability or injuries, geographical differences, and interracial inequalities. Therefore, future studies should include these variables to further understand how these factors affect healthcare payments.

CONCLUSIONS

This study had proved that the incidence of CHE among low-income households in Malaysia is low, implying that healthcare provision in the country had provided financial protection to the low-income households. However, the low incidence of CHE is not negligible especially considering the study was conducted among low-income households who are vulnerable to financial distress and poverty.

Several factors are found to predict CHE among low-income households; employment status of head of household, household size, presence of elderly, presence of child aged 5 years old and less, having any accident or medical insurance and hospitalisation among household members. Assimilating this knowledge in future planning of health intervention and policies is imperative to enable the provision of high-quality health services while protecting households from the unintended consequences of financial hardship. However, there is still much to learn with regards to CHE among Malaysian population. Therefore, we recommend future research to investigate the utilisation of health insurance among the low-income households and explore the coping mechanism of households burdened with CHE in order to better formulate future healthcare finance policies.

ACKNOWLEDGEMENTS

We would like to thank the Department of Statistics Malaysia (DOSM) for sharing data with the Universiti Putra Malaysia (UPM) Sultan Abdul Samad Library to enable the conduct of this research.

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Comparison of clinical efficacy and satisfaction of Tiotropium via Respimat® administration with and without a spacer in patient with Chronic Obstructive Pulmonary Disease: A randomized control trial

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ABSTRACT

Objective: This study assessed the delivery of tiotropium via Respimat® in addition to standard care of treatment among chronic obstructive pulmonary disease (COPD) patients. We study the efficacy, clinical outcome of handling inhaler device, rate of exacerbation and frequency of hospital admission of tiotropium via Respimat® with and without the use of a spacer (AeroChamber®).

Methods: Randomised, open-label study of COPD patients which was randomised into two groups: spacer or non-spacer groups using tiotropium via Respimat®. Treatment with their pre-existing inhalers continued. Subjects were assessed at weeks 0, and 8 for forced expiratory volume in 1 second (FEV1), COPD assessment tool (CAT), St. George's Respiratory Questionnaire (SGRQ), and satisfaction questionnaire.

Results: We enrolled 96 subjects: 49 in the spacer group and 47 in the non-spacer group. The mean predicted FEV1 in spacer group was 54.48% at baseline and 57.5l% at week 8: p=0.011. In the non-spacer groups, FEV_1 was 54.48% at baseline and 59.20% with a mean increment of 4.72 in both groups: p=0.002. There were no difference of exacerbation rates and hospital admission between both groups. At baseline, mean CAT score in the spacer group was 14.01 which improved to 9.80 (p<0.001) and 14.01 to 8.80 (p<0.001) in the non-spacer group. SGRQ total score reduced in both groups with mean difference of 3.1 (p<0.001) and 3.7: (p<0.001) at weeks 0 to 8.

Conclusion: There was no difference between exacerbation and hospital admissions between both groups. There was no difference in FEV1, CAT and SQRQ score using Tiotropium via Respimat® with or without a spacer.

KEYWORDS:
COPD, Tiotropium Respimat®, inhaler technique, FEV1, CAT, SGRQ satisfaction and quality of life.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic airflow limitation disease caused by exposure to noxious particles or gases.[1] It is the third leading cause of death globally.[1-3] In Malaysia, COPD is ranked as the fifth most common diagnosis of hospital admissions.[4] In the Asia Pacific region, tobacco smoking and air pollution remain the leading cause of COPD.[5]

The main goal of COPD treatment is to control symptoms and reduce exacerbations. Inhalers are the cornerstone of COPD treatment allowing delivery of the active treatment to the target site. The current inhalation devices are pressurised metered-dose inhalers (pMDIs), dry powder inhalers, and soft mist inhalers (SMIs).[1] Poor inhaler technique is a concern and is associated with an increased risk of exacerbation.[6-8]

The selection of inhaler device should be determined by the patients' disease, clinical setting and inhalation technique.[9] Other parameters to consider include patient's inhalation flow, the aerosol velocity, and the inhaled drug particle size.[10] Physical restrictions including weakness, declining vision, poor hearing, low inspiratory strength and decline in cognitive function can impair the ability to recall the correct inhaler techniques which can affect drug deposition in lung.[11,12]

A particle size between 2 and 5 microns has the greatest potential to be deposited throughout the bronchial tree.[13] Ideally a slow and deep inhalation (30L/min) is required for pMDI followed by breath hold pause of ≥4s and optimally up to 10 second.[13] A slow-moving velocity aerosol, with a smaller drug particle size, has achieved more than 50% total lung deposition and better penetration into the distal airway.[14,15]

For the majority of patients prescribed inhalers, poor respiratory effort, poor coordination and inadequate techniques remain a problem. spacers are able to help overcome patients with poor coordination. Spacers vary according to their volume or size, manufacture and propensity to become electrostatically charged, their mode of interface with the patient, and the presence or absence of valves and feedback device. Spacers allow deceleration of plume and obliterates the need for hand-mouth coordination thus making inhaler use easier and decreasing oropharyngeal deposition.[15,16]

This article was accepted: 06 June 2022
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Tiotropium via Respimat® is a SMI approved as a maintenance bronchodilator in 2007. It delivers treatment via a slow-moving fine liquid aerosol.[11,17] It produces fine and extra-fine particles, resulting in higher deposition in the smaller airways and less oropharynx deposition.[18-20]

Coordination needed for the usage of Respimat® inhaler has not been widely studied. The addition of a spacer to the delivery of tiotropium via Respimat® has not been shown to have additional benefits in a small Japanese study.[21] We aimed to study the efficacy, clinical outcome of handling inhaler device, rate of exacerbation, and frequency of hospital admission of tiotropium via Respimat® with and without the use of a AeroChamber®.

MATERIALS AND METHODS

This was a randomised, open label single centre study of outpatient COPD patients in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) conducted between September 2019 and February 2020. The study was approved by the Research Ethics Committee, Universiti Kebangsaan Malaysia, FF-2019-462. This research was registered with clinical trial number NCT04999930. The sample size calculation was performed by using Power and Sample software version 3.1.2 (Dupont & Plummer, 1997) comparing two proportion of exacerbation among spacer and non-spacer participants. We used the exacerbation rates based on the study by Faikh et al.[22] The total sample size calculated was 120 (60 subjects in each group), allowing 20% dropout rate). The power of the study was designed at level of 80%, at two-sided alpha level of 0.05.

Patients with a physician diagnosis of COPD were recruited prospectively from the outpatient clinic. We included the following patients: age more than 40 years, able to use inhaler medication and perform spirometry and no exacerbations in two months prior to recruitment.

Patients were excluded if they had a history of bronchial asthma or if they had a condition that could influence their ability to participate in the study; for example, if they have craniofacial anomalies, they are unable to perform or are contraindicated to do spirometry. Patients were allowed to continue with their usual inhalers during the study period. Following screening, baseline demographic data including age, gender, body-mass index (BMI), education level and race were recorded. Spirometry was performed by a trained technician using SpiroUSB (CareFusion).

The primary outcome was to compare the frequency of exacerbation and hospital admission using tiotropium via Respimat® with and without a spacer. For the purpose of this study, we use a similar type of spacer (AeroChamber Plus® Flow-Vu®) in our subjects. Secondary outcome was to examine mean difference in FEV1 between the treatment group, to identify and compare inhaler technique error between the group, to assess quality of life (SGRQ and CAT questionnaire) and to assess patient's satisfaction and preference, attitudes, and perceptions about their inhalers.

CAT score questionnaires were used as a tool to quantify patients' overall disease control. It is available in multiple languages depending on patient's preference.[23] In the SGRQ, a mean change score of four units is associated with slightly efficacious treatment, eight units for moderately efficacious change and 12 units for very efficacious treatment.[24] It is a score range from 0 to 100 with a higher score indicating the worse quality of life.

In our study, a COPD exacerbation is defined as a complex of lower respiratory events/symptoms (increase or new onset) related to underlying COPD, with a duration of three days or more requiring a change in treatment where a complex of lower respiratory events/symptoms is defined as at least two of the following: shortness of breath, sputum production, cough, wheezing chest tightness; and required changes in treatment including prescription of an antibiotic or systemic steroid or newly prescribed maintenance respiratory medication (bronchodilator and theophylline).

When performing spirometry, subjects were asked to blow out for at least 6 seconds according to the American Thoracic Society (ATS) criteria. This was performed at least three times and a maximum of eight tests depending on the quality of test. A minimum of three acceptable measurements were recorded for each subject, and the test will only be considered if the variation between the two best readings is less than 5%. The COPD assessment tool (CAT) and St. George's Respiratory Questionnaire (SGRQ) questionnaires were administered in either English, Chinese or Malay language depending on the subject's preference. The inhaler technique was assessed using a checklist documenting the adherence to manufacturers' directions for each inhaler. Patients were asked to demonstrate the use of their inhalers using the actual device. If incorrect technique was observed, the investigator would explain the corrections and ensure proper use.

Eligible subjects were then randomised using simple randomisation using numbered container into two groups: spacer or non-spacer, and both groups were counselled regarding inhaler technique. Patients were instructed that only SPIRIVA® RESPIMAT® was to be used with the AeroChamber®.

At weeks 0, and 8 the following were performed; spirometry to look at the forced expiratory volume in 1 second (FEV_1), COPD assessment tool (CAT), St. George's Respiratory Questionnaire (SGRQ), and satisfaction questionnaire. The satisfaction questionnaire was developed by the authors in a series of meetings. We used framework from Ogasawara et al.,[22] to decide on elements to be included in the questionnaire such as satisfaction level of inhalation with and without a spacer and regarding maintenance of the spacer. In the second phase, a pilot study was carried out to evaluate the feasibility and to modify the questionnaire accordingly.

Assessment of inhaler technique errors and counselling was performed periodically using phone calls. Inquiries regarding exacerbations, side effects and hospitalization if any were also asked during the phone calls.

Table I: Patients demographic and baseline characteristics in aero-chamber and non -aero-chamber group

Demographic variables		Tiotropium Respimat® with aero-chamber (Group A) (n=49) %	Tiotropium Respimat® without aero-chamber (Group B) (n=47) %	p-value
Age (mean±SD), years		73.00±8.76	68.81±9.26	0.110[a]
Body mass index, (mean±SD), kg/m^2		23.70±4.19	25.80±10.00	0.457[b]
Gender	Male	42 (85.7)	42 (89.4)	0.589c
	Female	7 (14.3)	5 (10.6)	
Races	Malay	20 (40.8)	21 (44.7)	0.584[d]
	Chinese	26 (53.1)	21 (44.7)	
	Indian	3 (6.1)	5 (10.6)	
Smoking status	Nonsmoker	9 (18.4)	5 (10.6)	0.361[c]
	Current smoker	7 (14.3)	3 (6.4)	
	Ex-smoker <10 years	15 (30.6)	18 (38.3)	
	Ex-smoker > 10 years	18 (36.7)	21 (44.7)	
Comorbidities	Nil	9 (18.4)	11 (23.4)	0.259[d]
	DM	1 (2.0)	4 (8.5)	
	HPT	22 (44.9)	13 (27.7)	
	DM + HPT	14 (28.6)	10 (21.3)	
	DM + HPT + IHD	1 (2.0)	4 (8.5)	
	HPT + IHD	2 (4.1)	2 (4.3)	
Number of maintenance inhaler	Single	24 (49.0)	19 (40.4)	0.399[c]
	Multiple	25 (51.0)	28 (59.6)	
Duration of COPD	<1 year	7 (14.3)	9 (19.1)	0.667[c]
	1 -5 year	21 (42.9)	16 (34.0)	
	5 - 10 year	14 (28.6)	12 (25.5)	
	> 11 year	7 (14.3)	10 (21.3)	
FEV1 percentage (mean±SD)	55.90±23.03	53.00±20.70	0.519a	
FVC percentage (mean±SD)	61.02±22.31	58.34±18.72	0.686a	
Gold stages	A	0(0)	0 (0)	0.749[c]
	B	22 (44.8)	21 (42.6)	
	C	22 (44.8)	20 (34.0)	
	D	5 (10.4)	6 (12.8)	
CAT score	Low (1-10)	9 (18.4)	13 (27.7)	0.250
	Medium (11-20)	31 (63.3)	31 (66.0)	
	High (21-30)	8 (16.3)	3 (6.4)	
	Very high (>30)	1 (2.0)	0 (0.0)	
mMRC	1	18 (36.7)	15 (31.9)	0.670c
	2	25 (51.0)	28 (59.6)	
	3	6 (12.2)	4 (8.5)	
	4	0 (0)	0 (0)	
SGRQ	Symptom	42.18±17.40	47.32±17.70	0.154[a]
	Activity	44.14±18.74	43.58±19.33	0.887[a]
	Impact	28.43±15.30	30.94±15.21	0.422[a]
	Total	35.63±14.76	37.48±14.32	0.536[a]
Number of exacerbations in the past year	0	33 (67.3)	36 (76.6)	0.771[d]
	1	10 (20.4)	7 (14.9)	
	2	4 (8.2)	3 (6.4)	
	3	2 (4.1)	1 (2.1)	
Number of admissions in the past year	0	48 (98.0)	45 (95.7)	0.613[d]
	1	1 (2.0)	2 (4.3)	
	2	0(0)	0(0)	

[a]Independent t test; [b]Mann Whitney test; [c]Pearson Chi-square; [d]Fisher's Exact test
DM: Diabetes Mellitus, HPT: Hypertension, IHD: Ischemic heart disease

Table II: Exacerbation and hospital admissions during study period of aero-chamber and non -aero-chamber Groups

Variables		Tiotropium Respimat® with Aerochamber n (%)	Tiotropium Respimat® without Aerochamber n (%)	p-value
Exacerbation	Yes	16 (16.7)	11 (11.4)	0.314a
	No	80 (83.3)	85 (88.6)	
Hospital admission	Yes	1 (1.1)	1 (1.1)	>0.950 b
	No	95 (98.9)	95 (98.9)	

[a]Pearson Chi square; [b]Fisher's Exact test

Table III: Comparison of FEV_1, CAT, SGRQ within AeroChamber® group and non-AeroChamber® group and satisfaction between the two groups

Variables	Tiotropium Respimat® with aero-chamber			Tiotropium Respimat® without aero-chamber		
	Before mean (SD)	After mean (SD)	p value	Before mean (SD)	After mean (SD)	p-value
FEV_1	54.48 (21.86)	57.55 (21.03)	0.011	54.48 (21.86)	59.20 (21.09)	0.002
CAT	14.01 (5.13)	9.80 (3.64)	<0.001	14.01 (5.13)	8.80 (3.90)	<0.001
SGRQ Symptom	44.70 (17.64)	34.73 (13.94)	<0.001	44.70 (17.64)	29.04 (15.19)	<0.001
SGRQ activity	43.87 (18.93)	33.34 (14.41)	<0.001	43.87 (18.93)	28.40 (13.53)	<0.001
SGRQ Impact	29.66 (15.23)	20.25 (12.47)	<0.001	29.66 (15.23)	17.14 (11.63)	<0.001
SGRQ Total	36.54 (14.50)	33.77 (108.09)	<0.001	36.54 (14.50)	26.61 (11.41)	0.805
Satisfaction	2.91 (0.18)	3.12 (0.20)	<0.001	3.09 (0.22)	3.25 (0.17)	<0.001

Association of the mean difference at baseline and week 8 between 2 groups

Variables	Tiotropium Respimat® with aerochamber mean difference (SD)	Tiotropium Respimat® without aerochamber mean difference (SD)	p value
FEV_1	-3.07 (11.64)	-4.72 (14.21)	0.3799
CAT	4.21 (3.32)	5.21 (4.03)	0.0621
SGRQ Symptoms	9.96 (16.37)	15.65 (20.44	0.0345*
SGRQ Activity	10.53 (14.65)	15.47 (18.26)	0.0400*
SGRQ Impact	9.41 (14.67)	12.52 (15.75)	0.1585
SGRQ Total	2.77 (2.33)	9.92 (11.93)	<0.0001*
Satisfaction	-0.21 (0.21)	-0.16 (0.19)	<0.0001*

FEV1: Forced expiratory volume in 1s; CAT: COPD assessment test; SGRQ: St George's Respiratory Questionnaire, p-value <0.001 is significant, *Paired T-test

STATISTICAL ANALYSIS

All data were analysed using Statistical Package for Social Sciences (SPSS) version 25.0. The continuous variables were tested with Student t test for normal distribution and Mann-Whitney U test for non-normal distribution to compare between the two groups: spacer and non-spacer. The categorical data were tested with Pearson Chi-square test and Fisher exact test. The results of the data between the two groups were analysed using Independent-sample t-test or its equivalent non-parametric Mann-Whitney U test for parameter non-normal distribution. Paired t-test were used to analysed data in each group. Statistical significance was declared when $p<0.05$.

RESULTS

A total of 137 COPD patients were screened between September 2019 and February 2020. Ninety-six patients fulfilled the inclusion criteria and consented to be involved in the study.

The mean age was 70.95±9.21 years and the majority were men (84, 85.7%). Thirty-nine (40.6%) were current smokers and 33 (34.4%) were lifelong non-smokers. Only 14.6% had no co-morbidities. About 67% of subjects had at least ≥2 comorbidities. More than half the study population had multiple numbers of maintenance inhalers. Nearly half (44.8%) had COPD diagnosis of ≥5 years. Demographic details as well as pulmonary function test results, CAT and SGRQ score were listed in Table I.

There was no association between spacer usage with both exacerbation and hospital admission. During the study period, 16 (16.7%) participants in the spacer group and 11 (11.4%) participants in the non-spacer experienced exacerbations of symptoms (Table II).

The predicted mean percentage FEV_1 was 54.48±21.86%. Majority (77.15) had CAT Score at ≥11. In the past year, 71.9% did not experience any exacerbations and only 3.1% had one hospital admission in the last year.

There was a statistically significant difference between baseline and 8 weeks of treatment in both groups for the following: CAT, SGRQ and satisfaction FEV_1 mean difference of -3.07 in the spacer group and -4.72 in the non-spacer group (Table III). The mean changes in FEV_1 were -1% after 8 weeks of tiotropium via Respimat®.

The mean percentage change in the trough FEV_1 was -3.07% after 8 weeks of treatment in the tiotropium via Respimat® treatment administered with a spacer and -4.72 without a spacer. There was no significant difference in the mean percentage change FEV_1 between tiotropium via Respimat® therapy delivered with and without a spacer (Table III).

There was also no significant difference between tiotropium via Respimat® therapy with and without a spacer with respect to mean percentage difference in CAT score at week 8. However, there was a significant difference in the mean percentage change of SGRQ (symptoms and activity and total) between tiotropium therapy delivered with and without a spacer (Table III).

Inhaler satisfaction scores using tiotropium via Respimat® with and without a spacer at baseline and at 8 weeks are shown in Table IV. At baseline, 47 (49%) subjects had difficulty to assemble tiotropium via Respimat®. The numbers decreased to 22 (22.9%) at week 8. About 67 (69.8%) subjects in the non-spacer group and 33 (34.4%) subjects in with the spacer group found the use of inhaler fairly easy. More than half (61.5%) at baseline and 67.7% at week 8 were not keen to bring along their spacers out of their home (Table IV).

The number of patients who were confident using tiotropium via Respimat® increased from 1 (1%) prior to counselling to 77 (80.2%) at week 8. More than 90% of subjects were

Table IV: Satisfaction of using Tiotropium Respimat® with and without aero-chamber at baseline and at week 8

Questions	Baseline (Week 1)					At Week 8				
	Very n (%)	Fairly n (%)	Somewhat n (%)	Not very n (%)	Hardly at all n (%)	Very n (%)	Fairly n (%)	Somewhat n (%)	Not very n (%)	Hardly at all n (%)
1. How easy was it to assemble the SMI?	2 (2.1)	42 (43.8)	47 (49.0)	5 (5.2)	0 (0.0)	1 (1.0)	72 (75.0)	22 (22.9)	1 (1.0)	0 (0.0)
2. How easy did you find the use SMI?	11 (11.5)	67 (69.8)	18 (18.8)	0 (0.0)	0 (0.0)	3 (3.1)	43 (44.8)	37 (38.5)	13 (13.5)	0 (0.0)
3. How easy did you find the use of SMI with aero-chamber?	1 (1.0)	28 (29.2)	47 (49.0)	19 (19.8)	1 (1.0)	1 (1.0)	33 (34.4)	19 (19.8)	42 (43.8)	1 (1.0)
4. How likely are you to bring along your aero-chamber when you are outside your home?	0 (0.0)	3 (3.1)	59 (61.5)	34 (35.4)	0 (0.0)	0 (0.0)	4 (4.2)	65 (67.7)	27 (28.1)	0 (0.0)
5. How confident are you in using your SMI?	0 (0.0)	1 (1.0)	11 (11.5)	81 (84.4)	3 (3.1)	0 (0.0)	77(80.2)	17(17.7)	2 (2.1)	0 (0.0)
6. After our counselling session, how confident are you now in using your SMI?	1 (1.0)	64(66.7)	30 (31.3)	1 (1.0)	0 (0.0)	51 (53.1)	44 (45.8)	1 (1.0)	0 (0.0)	0 (0.0)
7. How confident are you in maintenance of your aero-chamber?	0 (0.0)	4 (4.2)	90 (93.8)	2 (2.1)	0 (0.0)	0 (0.0)	4 (4.2)	91 (94.8)	1 (1.0)	0 (0.0)
8. Overall, how satisfied are you with the SMI?	0 (0.0)	38 (39.6)	58 (60.4)	0 (0.0)	0 (0.0)	3 (3.1)	75 (78.1)	18 (18.8)	0 (0.0)	0 (0.0)

somewhat confident in the maintenance of AeroChamber® at baseline and week 8. Satisfaction of tiotropium via Respimat® increased from 39.6% to 78.1% after 8 weeks (Table IV).

We assessed inhaler critical errors at baseline and at 8 weeks' treatment. The three common errors of tiotropium via Respimat® in the non-spacer group are : (1) failure to exhale prior to use inhaler - 30 (31.2%); (2) failure to maintain a good seal for 5 breaths after pressing SMI - 29 (30.5%); (3) failure to hold upright with cap close - 17 (17.7%). Common errors of SMI with spacer usage are (1) failure to check the spacer for foreign objects - 35 (36.5%), (2) failure to inhale slowly and deeply - 33 (34.4%), (3) failure to slow down inhalation despite whistling sound - 31 (32.3%).

DISCUSSION

Successful treatment of COPD depends on the effective delivery of bronchodilators to the lungs. Bronchodilators used in stable COPD include SABA, SAMA, LABA and LAMA. Inhalers are the mode of delivery and different inhalers have distinct characteristics which can affect the administration of the drug.

Tiotropium was the first LAMA available for COPD treatment. Tiotropium via Respimat® was approved as a COPD maintenance bronchodilator in 2007 in Europe and in 2014 in the United States and Canada. The use of tiotropium via Respimat® has been shown to increase in FEV_1 and FVC from as early as 24 weeks and reduce both moderate and severe exacerbations.[25,26]

Spacers cause deceleration of aerosol and decrease oropharyngeal deposition as much as 90% and decrease the need for coordination between hand and actuation when used with pMDI. Because of these factors, the use of spacers is established in the treatment paradigms.

While data on the benefit of pMDI and AeroChamber® is well documented, the benefit of the addition of AeroChamber® to the Respimat® device is less studied. To our knowledge, this is the first study in Malaysia to study the benefit of tiotropium inhalation therapy using Respimat®. with the addition of a AeroChamber® in terms of clinical efficacy (FEV1, CAT Score and SGRQ Score), exacerbation and patient satisfaction using inhaler with/out AeroChamber®.

COPD affects mainly males. This is likely related to the smoking habit as smoking causes COPD and it is a predominant male habit. Previous local study done in Malaysia also showed male predominance.[27] In our study, 87. 5% were males and 40% were current smokers.

The majority of patients were in GOLD B (43.7%) and followed by GOLD C (39.5%). We had no patients in Gold A as we are a tertiary referral center. In our study, 17.7% reported one exacerbation in the last 1 year. In terms of symptoms, only 12.5% were highly symptomatic using the CAT score.

We found that the addition of AeroChamber® to tiotropium via Respimat® had no significant improvement in percentage

FEV_1. A small Japanese study involving 20 patients with tiotropium via Respimat® using AeroChamber® and non-AeroChamber® showed similar findings in terms of FEV_1.[21] This may be due to the short duration of both our study (8 weeks) and the Japanese study (2 weeks); as the earliest improvement of FEV_1 was reported at 24 weeks.[25,26]

The COPD assessment tool (CAT) and St. George's Respiratory Questionnaire (SGRQ) were used to assess severity and quality of life. We found improvement in symptoms at the end of 8 weeks of intervention. The mean change in CAT score reduced from 14.01 to 9.80 in the AeroChamber® group and 14.01 to 8.80 in the non-AeroChamber® group. Subjects had regular phone calls and were reminded to use their inhalers and had their technique corrected. This may have contributed to better adherence to the medication.

In the SGRQ scores, there was a statistically significant difference between baseline and 8 weeks of treatment for symptoms, activity, impact, and total score in both groups. The mean change in the domain of symptoms, activity, and impact was more than 12 in the non-AeroChamber® versus AeroChamber® group where the mean change ranged from 9.41 to 9.97. The impact of AeroChamber® appeared to lessen the improvement in the group.
There was no association between the use of AeroChamber® with exacerbations and hospital admission. Twenty-seven patients (27%) had reported exacerbation during the study period. However, we may have missed some symptomatic events as this was based purely on patient's recall. Some subjects may have been reluctant to declare their symptoms accurately to medical staff.

Our study had a lower exacerbation rate compared to other studies. This may be due to our inclusion criteria. Part of the study was conducted during pandemic COVID 19 with strict movement control orders. This may have led to a decrease in infection-related exacerbation.

Inhaler errors affect drug delivery.[28] Studies have shown that inhaler technique errors are common and occur in up to 90% of patients regardless of inhaler device. A real-world study showed that when patients make a single critical inhaler error there is a risk of COPD exacerbation.[29] When invited to demonstrate their tiotropium via Respimat® inhaler technique, at baseline, 100% subjects made ≥1 device use errors.[29] The majority of subjects were unable to ensure a tight seal with lips around the mouthpiece and when mouthpiece was inserted into the AeroChamber®. The other common error was a failure to exhale prior to inhaler use. Device errors in tiotropium via Respimat® have been reported to occur in 6 out of 10 patients. In our study, there was an improvement in the number of errors made at each step of tiotropium via Respimat® at 8 weeks. The number of errors decreased after counselling which was done at baseline and at regular intervals during the 8-week study period.[30]

COPD exacerbations frequently related to poor inhalation techniques potentially impact the quality of life.[12,25] Multiple studies done previously had shown the correlations.[13,25] The decrease in the number of errors translates to a decrease in COPD exacerbations. Our study highlights that in addition to prescribing inhalers, counselling and correction of inhaler technique should also be emphasized in COPD management. This corresponds to one study that showed that without counselling, patients demonstrating correct technique declined by 39% on subsequent visit.[31]

None of our patients had rheumatological comorbidities. Despite that, 49% of subjects had difficulty assembling tiotropium via Respimat® at baseline. Nearly 70% preferred using tiotropium Respimat® without the AeroChamber®. Our patients were using AeroChamber® device at home, but on further questioning, they appeared reluctant to bring the AeroChamber® outside their home citing bulkiness as one of the main reasons. Other studies have also shown a poor uptake of AeroChamber®.[32]

However, we found that with regular counselling, their confidence level to assemble and use SMI improved at week 8 in both groups. Their overall satisfaction using tiotropium Respimat® improved from 39.6% to 78.1%. Other studies have shown that the reported satisfaction rate handling tiotropium Respimat® device from satisfaction rate 63.5-84.3%.[33,34]

Subjects did not find the use of tiotropium Respimat® with AeroChamber® easy. About 49% of subjects found the use of tiotropium Respimat® with AeroChamber® somewhat easy, however at the end of 8 weeks, only 19.8% found it useful. With regards to maintenance of AeroChamber®, less than 5% of subjects were fairly confident. These issues may lead to intentional non-compliance where the patients refrain from using the AeroChamber® or only uses it from time to time.

Our study attempts to mimic real-world use of Spiriva Respimat with AeroChamber®. In our study, subjects were allowed to continue their usual bronchodilators; counselling and reminders were done with a simple phone call. We showed no reduction of efficacy of tiotropium Respimat® with AeroChamber®. The design of our study allowed an accurate short-term recall allowing an accurate representation of patient's satisfaction as each patient experienced the use of tiotropium Respimat® with and without AeroChamber®. These findings suggest that in a subset of patient with poor hand-mouth coordination; AeroChamber® with tiotropium Respimat® is as efficacious in delivering drugs.

This study has several limitations as it is a single-centre study. We did not use the diary to document patient's adherence to AeroChamber®. Therefore, we might have underestimated the true adherence. During the non-intervention period of the study, there were no phone calls and we were unable to monitor and ensure that they were not using AeroChamber®. Phone inquiry was performed on exacerbation which might not be accurate is another limitation of the study.

In our study, the non-AeroChamber® group reported higher satisfaction scores and better quality of life. We conclude that there was no difference of exacerbation and hospital admission between both groups. Tiotropium Respimat® using AeroChamber® does not offer additional benefit in terms of FEV1, CAT and SQRQ score in severe COPD patients. However, we recommend that adding an AeroChamber® to Tiotropium Respimat® may be suitable for a subset of patients with poor and-mouth coordination.

ACKNOWLEDGEMENT

This study received a fundamental grant from Universiti Kebangsaan Malaysia: FF-2019-462.

DISCLOSURE STATEMENT:

The authors declare that they have no competing interests. Appropriate written informed consent was obtained for the publication of this study.

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ORIGINAL ARTICLE

Sexual characteristics, knowledge on human papillomavirus-related diseases and its associated factors among high-risk men

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ABSTRACT

Introduction: Human papillomavirus (HPV) infection is sexually transmitted and responsible for anogenital warts and malignancies. HPV-related disease awareness among high-risk men in Malaysia remains unknown. The objective of this study was to assess sexual characteristics and HPV knowledge among high-risk men.

Materials and Methods: A total of 194 men between ages 18 and 45 years from the HIV and STD clinics of a tertiary hospital and six Health Clinics in Perak participated in this study. Knowledge of HPV was assessed using a self-administered questionnaire.

Results: Majority of participants were Malays (47.4%) and had tertiary education (54.1%). Most of them (76.5%) were homosexual and practiced the versatile sexual role (69.9%). Majority engaged in oral (72.2%) and anal sex (58.2%). Only one-third of them (30.8%) used condom consistently. Only 14.4% of the study participants had adequate knowledge of HPV. Men who practiced oral sex and had previous STD had adequate knowledge of HPV. Those who practiced oral sex were 3.9 times more likely to have adequate knowledge of HPV.

Conclusion: Our study shows that most participants have high-risk sexual behaviour. These men also have poor knowledge of HPV-related diseases. This may be a barrier to implement preventive strategies and reduce HPV-related disease and malignancies among them. Counselling regarding HPV, for men attending the HIV and STD clinics may improve patient's awareness and knowledge on HPV-related diseases and promote HPV vaccination uptake.

KEYWORDS:
HPV infection, knowledge, high-risk men, sexual characteristics

INTRODUCTION

Human papillomavirus (HPV) infection is one of the most prevalent sexually transmitted infection worldwide.[1] HPV subtypes 6 and 11 are responsible for anogenital and respiratory papilloma (warts) while infection with subtypes 16 and 18 are responsible for malignancies.[2] Although HPV infection is more popularly known to be associated with cervical cancers among women, studies looking at HPV-related malignancies have shown an association with anal and penile cancers among men with HPV, acquired through sexual contact.[3-5] The high-risk subtypes 16 and 18 have been detected in 88% of anal cancers, 50% of penile cancers, and in about 26% of oropharyngeal cancers.[6] The risk factors for acquiring HPV infection include multiple sexual partners, early age of sexual initiation, receptive anal intercourse, unprotected sex, previous history of sexually transmitted diseases, and HIV-positive homosexual men.[7,8]

Studies in Puerto Rico, Italy and The United States of America (USA) have found a lack in knowledge regarding HPV, risk of acquiring HPV infection, HPV-related diseases and awareness of HPV vaccine among homosexual and bisexual men and women.[1,9,10] This lack of knowledge regarding HPV infection is an obstacle to preventive efforts such as safe sex advice and HPV vaccination uptake. The lack of knowledge regarding HPV-related malignancies can increase morbidity and mortality due to these conditions as people are unaware of underlying risks associated with HPV. Despite the high rates of HPV infection amongst men and rising incidences of anal and penile cancers attributed to its infection, health promotion, and preventive strategies targeting high-risk men in Malaysia and other countries like Hong Kong are still lacking.[6,11] However, preventive strategies against HPV-related cervical cancer for women in Malaysia are well established.

Since the women in Malaysia have well-established preventive measures against HPV-related malignancies, it is now time to shift the focus to men. Assessing men's knowledge and awareness of HPV infections will foster successful preventive strategies as some of these subtypes are vaccine preventable. The aim of this study is to assess the sexual characteristics, knowledge regarding HPV-related diseases and its associated factors among high-risk men. This information could provide substantial insight regarding the high-risk men and facilitate policy planning regarding vaccine-preventable diseases among men in Malaysia.

MATERIALS AND METHODS

A cross-sectional study was conducted from December 2020 to April 2021 among men attending the HIV and STD clinic at Hospital Raja Permaisuri Bainun (HRPB) Ipoh and six Health Clinics in Kinta district, Perak. The sample size was calculated using the Kish Formula using the prevalance of

This article was accepted: 07 June 2022
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adequate knowledge of HPV infection of 29.3%;[1] 95% confidence interval and 7% absolute precision. An additional 20% was added for possible incomplete response, giving a final sample size of 194. Male participants aged 18 years and above who understood English or Bahasa Malaysia were invited to participate in this study using convenience sampling when they registered for their scheduled appointment. Those who agreed to participate were briefed regarding the study and an anonymous written consent was obtained.

The main tool used in this study was a self-administered questionnaire from a previous study by Colon Lopez el al.[1] The original questionnaire was subjected to cultural and social adaptation to suit the local population by an expert panel consisting of the researcher, a consultant family medicine specialist, consultant dermatologist, and infectious disease physician. The questionnaire was then translated forwards and backwards by two linguists. The final bilingual questionnaire was then subjected to face validation. The Cronbach Alpha value of the 14-item scale for knowledge was 0.876.

The questionnaire consists of total 31 statements in two parts. The first part of the questionnaire contained participant's demographic data (6 questions) and sexual characteristics (11 questions). Consistent use of condom was defined as the use of condom at every sexual encounter in the last 1 year.[12] The second part assessed participant's knowledge regarding HPV infection using 14 statements where participants were instructed to select one of the three options, "Yes", "No", or "Don't know" for each item. One point was allotted for each correct response while the incorrect or "don't know" responses was scored zero. Hence, the minimum and maximum scores were zero (0%) and 14 (100%), respectively. Adequate knowledge was defined as having at least 10 correct responses out of the 14 (which is 70%) based on the original cut-off score of the original questionnaire.[1] The cut-off value of 70% was taken as good knowledge based on the expectant knowledge according to the Central Disease Control on HPV information pamphlet content as there was no local public awareness pamphlet on HPV. All participants were given this pamphlet (translated to Bahasa Malaysia) upon completing the questionnaire to create awareness regarding HPV infection among men.

A pilot study was done and there were no problems in the process of data collection. Data were then collected and analysed using "Statistical Package for Social Sciences (SPSS)" version 26 (SPSS Inc., Chicago, IL, USA). Descriptive analysis was used to describe knowledge on HPV while Chi Square and Mann–Whitney U tests, were used to describe the association between demographic and sexual characteristics and knowledge of HPV.

This research was approved by the Research and Ethics Committee of Universiti Kebangsaan Malaysia Medical Centre (FF- 2020-012) and registered with the National Medical Research Registration (NMRR-19-4086-51097).

RESULTS

A total of 194 participants completed the questionnaire. The median age of participants was 31 years (IQR: 12) and they were mainly Malays (47.4%, n=92). Participants mostly had tertiary education (54.1%, n=105) and were from the low-income group (86.6%, n=168).

The median age of initiating sexual activities was 19 years (IQR: 3). Most (66.5%, n=129) participants had male partners (homosexual) practiced anal sex (58.2%, n=113) and assumed the versatile sexual role (69.9%, n=79). HIV (80.9%, n=157) and syphilis (29.9%, n=58) were the two commonly acquired sexually transmitted diseases. More than half (60.3%, n=117) of the participants were sexually active with about one-third of them (28.9%, n=56) had more than one sexual partner. A large majority (82.9 %, n=97) of participants who were sexually active used condom but only one-third 30.8% (n=36) of them used it consistently.

The mean score for knowledge of HPV-related diseases was 3.4 (SD ± 4.35). Only 14.4% (n=28) men had adequate knowledge (knowledge score >70%) regarding HPV. The best score for knowledge was for the statement HPV can spread through sex while the lowest was the statement "Some HPV type can disappear without treatment". The knowledge score was almost similar across all domains (Table I).

There was no association between participant's demographic characteristics and adequate HPV knowledge (Table II).

Testing the association between adequate knowledge of HPV and sexual characteristics, showed that participants who practiced oral sex and those with a previous history of sexually transmitted diseases have association with knowledge regarding HPV (Table III).

Independent variables with p value <0.25 were further selected for multivariate logistic regression analysis adjusted for employment status, oral sex practise, previous history gonorrhoea, and syphilis. The regression model reasonably fit well. There were no multicollinearity and interaction between the independent variables tested. It was found that participants who practiced oral sex were found to be 3.90 times more likely to have adequate knowledge regarding HPV (adjusted Odds Ratio, aOR 3.90; 95% Confidence Intervals, 95%CI: 1.06, 14.28). The Nagelkerke R square value for this model is 0.199 (Table IV).

DISCUSSION

Most of our study participants received higher education (54.1%); however, the majority were from the lower-income group (86.6%) and were not married (80.9%). Similar study done amongst HIV/STD male clinic attendees in China also showed that most study participants were single (64.5%) and from the lower and middle-income categories (83.9%).[13] Low socio-economic status and unmarried status have been linked with risky sexual behaviour, HPV infection and other STDs.[14,15] Those from low-economic levels tend to have increased social risk factors such as drug abuse and high-risk sexual behaviours, while those who are unmarried possibly engage in multiple sexual partnerships both of which

Table I: Knowledge on HPV and related diseases

Items	Frequency (n)	Correct response (%)
Nature of HPV infection		
There are many types of HPV	39	20.1
Some HPV type can disappear without treatment	24	12.4
Risk factors for HPV infection		
The more sexual partner I have, the higher my risk of getting HPV	71	36.6
Using condom can fully protect from HPV infection	46	23.7
Transmission of HPV infection		
HPV can spread through sex	73	37.6
I can infect my partner with HPV even though I am asymptomatic	56	28.9
Genital HPV can spread by skin-to-skin contact	30	15.5
HPV-related benign diseases		
HPV can cause genital warts in the anus	58	29.9
HPV can cause genital warts in the penis	57	29.4
Genital warts are caused by HPV	54	27.8
HPV-related malignancies		
HPV can cause cervical cancer	52	26.8
HPV can cause cancer of anus	51	26.3
HPV can cause cancer of penis	40	20.6
HPV can cause cancer of the mouth	34	17.5

Table II: Association between sociodemographic characteristics and adequate HPV knowledge

Variables	Frequency % (n)	Adequate HPV knowledge (N=194)		
		No % (n)	Yes % (n)	p-value
Ethnicity				0.909
Malay	47.4 (92)	47.6 (79)	46.4 (13)	
Non-Malay	52.6 (102)	52.4 (87)	53.6 (15)	
Education Level				0.151
School (primary and secondary)	45.9 (89)	48.2 (80)	32.1 (9)	
Tertiary	54.1 (105)	51.8 (86)	67.9 (19)	
Employment status				*0.179
Employed	83.5 (162)	81.9 (136)	92.9 (26)	
Unemployed	16.5 (32)	18.1 (30)	7.1 (2)	
Monthly income				*0.662
Low	86.6 (168)	85.5 (142)	92.9 (26)	
Middle	12.4 (24)	13.3 (22)	7.1 (2)	
High	1.0 (2)	1.2 (2)	0.0 (0)	
Marital status				*0.262
Unmarried	84.5 (164)	83.1 (138)	92.9 (26)	
Married	15.5 (30)	16.9 (28)	7.1 (2)	

*Fisher Exact Test was used. p-value < 0.05 is significant.

increase the risk of acquiring STDs.

Our study found that the median age of initiating sexual activity was fairly young (19 years; IQR: 3) and is similar to other studies done among high-risk men.[16,17] Early initiation of sexual activities at the stage where there is a lack of maturity and judgement predisposes to risky sexual behaviour such as unprotected sex, substance abuse, and multiple sexual partners eventually leading to higher incidences of HPV infection and other STDs.[18]

This study found a high rate of men who have sex with men (MSM) (76.5 %) and HIV infection (80.9%). Currently, MSM practice among the HIV population in Malaysia is about 21.6%.[19] This is a major concern, as concomitant HIV and HPV infection are responsible for retention of HPV in the body in contrast to people with normal immune system who have a chance for spontaneous elimination of HPV. Retention of HPV among people with HIV predisposes them to a higher risk of developing HPV-related malignancies due to persistent infection with HPV.[8]

More than half of our study participants practised anal sex with a large majority (87%) of them practicing anal receptive role. This is consistent with previous studies in China which reported that receptive anal sex practice was prevalent amongst MSM attending HIV and STD clinics (52%–66.7%).[13,17] Oral sex was also widely practised by the majority of our participants (72.2%) as also found by an earlier study.[20] This is of concern as both receptive anal intercourse and oral sex predisposes to anal cancer and oropharyngeal cancers, respectively. The incidences of both malignancies are on the rise, especially among MSM and male HIV population, attributed to their sexual practices.[6]

Almost one-third participants (28.9%, n=56) in our study had multiple sexual partners. This is less, compared to earlier data from Malaysia, Thailand, and Ireland where the percentages were more than 60%.[21-23] The apparent low figure in our study could be attributed to the Covid-19 pandemic as data were collected during the government's implementation of Movement Control Order (MCO) where social gatherings were restricted in effort to curb the pandemic. Additionally, our study also found that consistent use of condoms among sexually active participants were low (30.3%). Other parts of

Table III: Association between sexual characteristics and adequate HPV knowledge

Variables	Frequency % (n)	Adequate HPV Knowledge (N=194)		
		No % (n)	Yes % (n)	p-value
Sexual orientation				0.303
MSM	66.5 (129)	65.1 (108)	75.0 (21)	
Non-MSM	33.5 (65)	34.9 (58)	25.0 (7)	
Number of sexual partners (last 12 months)				0.128
None	39.7 (77)	42.2 (70)	25.0 (7)	
One partner	31.4 (61)	28.9 (48)	46.4 (13)	
Multiple partners	28.9 (56)	28.9 (48)	28.6 (8)	
Condom use (last 12 months) (n=117)				*0.522
No	17.1 (20)	18.8 (18)	9.5 (2)	
Yes	82.9 (97)	81.3 (78)	90.5 (19)	
Sexual practice				
Oral sex				
Yes	72.2 (140)	69.3 (115)	89.3 (25)	0.038
No	27.8 (54)	30.7 (51)	10.7 (3)	
Anal Sex				
Yes	58.2 (113)	57.2 (95)	64.3 (18)	0.539
No	41.8 (81)	42.8 (71)	35.7 (10)	
Role of anal sex				
Receptive	87.6 (99)	86.3 (82)	94.4 (17)	*0.463
Non-Receptive	12.4 (14)	13.7 (13)	5.6 (1)	
History of sexually transmitted diseases				
HIV				
Yes	80.9 (157)	81.3 (135)	78.6 (22)	*0.646
No	16.5 (32)	15.7 (26)	21.4 (6)	
Unsure	2.6 (5)	3.0 (5)	0.0 (0)	
Syphilis				
Yes	29.9 (58)	31.3 (52)	21.4 (6)	0.028
No	49.0 (95)	45.2 (75)	71.4 (20)	
Unsure	21.1 (41)	23.5 (39)	7.1 (2)	
Genital Warts				
Yes	13.9 (27)	12.0 (20)	25.0 (7)	*0.005
No	56.7 (110)	54.8 (91)	19 (67.0)	
Unsure	29.4 (57)	33.1 (55)	7.1 (2)	
Gonorrhoea				
Yes	7.7 (15)	6.0 (10)	17.9 (5)	*0.001
No	60.8 (118)	58.4 (97)	75.0 (21)	
Unsure	31.4 (61)	35.5 (59)	7.1 (2)	
Chlamydia				
Yes	2.6 (5)	2.4 (4)	3.6 (1)	*0.003
No	64.4 (125)	60.2 (100)	89.3 (25)	
Unsure	33.0 (62)	37.3 (62)	7.1 (2)	
Herpes				
Yes	2.1 (4)	1.8 (3)	3.6 (1)	*0.003
No	66.0 (128)	62.0 (103)	89.3 (25)	
Unsure	32.0 (62)	36.1 (60)	7.1 (2)	

*Fisher Exact Test was used. p-value <0.05 is significant

the world such as China and Thailand show a wide range of poor compliance to condom use among a similar population (13.3-57.3%).[13,22] An earlier study done among sexually active Malaysians revealed that inconsistent condom use was attributed to low awareness and negative perception of condom use.[24] Having multiple sexual partners and unprotected sex are common risk factors for sexually transmitted diseases, including HPV.

Our study also found that only 14.4% of participants had adequate knowledge regarding HPV infection. This is much lower compared to an earlier study done on a similar population in Puerto Rico (29.3%).[1] Although public campaigns on cervical cancer and its prevention have been promoted in Malaysia over many years, only about 25% of participants knew about this condition, reflecting a lack of awareness among men. An earlier local study discovered that only 36.5% of men had knowledge of HPV-related cervical cancer in women.[25,26] This shows that Malaysian men in general have a lack of awareness HPV-related diseases. They may be under the assumption that HPV infection affects woman as the current practice is to promote HPV screening and vaccination for women. Additionally, less than one-third of the participants knew that genital warts are caused by HPV, even though it is a commonly treated condition in STD clinic with high rates of recurrence.[22] The mean scores for knowledge items on the HPV-related malignancies in men were also poor. Perhaps, the absence of policy on HPV vaccination for men in Malaysia and the relative rarity of HPV-related cancers amongst them, may have further contributed to the scarcity of public information on HPV among men.

Previous studies have shown variable relationships between previous exposure to STD and knowledge of HPV where some showed positive or no associations. Studies from Puerto Rico

Table IV: Multivariate regression analysis for factors associated with adequate HPV knowledge

Variable	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Oral sex				
Yes	3.67 (1.07; 12.80)	0.04	3.90 (1.06; 14.28)	0.04*
No	(1)		(1)	
Gonorrhoea				
Yes	2.31 (0.72; 7.46)	0.16	2.75 (0.74; 19.27)	0.13
Unsure	0.16 (0.04; 0.69)	0.01	0.21 (0.02; 2.22)	0.20
No	(1)		(1)	
Syphilis				
Yes	0.43 (0.16; 1.15)	0.09	0.40 (0.13; 1.19)	0.10
Unsure	0.19 (0.04; 0.87)	0.03	0.70 (0.06; 7.81)	0.77
No	(1)		(1)	
Employ				
Yes	2.87 (0.65; 12.74)	0.17	3.44 (0.73; 16.25)	0.12
No	(1)		(1)	

Reference group. p-value <0.05 is significant, .* multiple binary logistic regression (MLogR), OR, Odds Ratio, 95%CI, 95% Confidence Intervals

and China did not find any significant association between HIV status and knowledge of HPV while one study amongst MSM in Florida found a positive association between HIV and better knowledge of HPV.[1,7,27] The possible explanation for better HPV knowledge among those with HIV or previous STD is that once diagnosed with an STD, these high-risk individuals would have received counselling regarding other STDs which include HPV as part of management to prevent future STDs. However, the participants with HIV in our study did show better knowledge of HPV. Hence, information regarding HPV and other STD should be offered during counselling upon diagnosis of HIV and STDs to increase awareness and as an effort to prevent future STDs.

Although genital wart is caused by HPV, having genital warts was not associated with adequate knowledge of HPV in our study. Meanwhile, a similar study by Colon-Lopez et al., showed an association between knowledge of HPV and diagnosis of herpes, while the history of genital warts only showed a marginal association. These findings suggest a possible lack of HPV-related counselling for HIV/STD-infected men during treatment for STD by their healthcare providers.

The current study found that men who engage in oral sex are almost four times more likely to have adequate knowledge of HPV. An earlier study in Bahamas also showed better awareness of HPV infection among youth who practised oral sex.[28] This is probably because those who engaged in oral sex would probably have a higher self-perceived risk of HPV hence better knowledge of HPV. Association between oral sex with higher self-perceived risk and awareness of HIV was also seen amongst heterosexual men in China.[29] It was also demonstrated that knowledge on oral sex and HPV-related oropharyngeal cancer amongst youth was associated with decreased willingness to engage in oral sex.[30]

Almost 66% of our study participants were MSM; however, we did not find any association between their sexual practice and knowledge of HPV although studies from other countries demonstrated better knowledge and awareness of HPV amongst this group.[1,9] MSM community in Malaysia has grown larger over the years and would benefit greatly from the targeted HPV vaccination in men.[20] This community benefits least from the herd immunity created through female HPV vaccination.[31] Imparting knowledge regarding HPV-related disease, appropriate preventive strategies such as safe sex practice advice and information regarding HPV vaccination could provide great health benefits for these high-risk men. These strategies could be an added advantage if initiated at the STD and HIV clinics. In fact, targeted HPV vaccination for MSM population has proven to be more cost-effective and confers greater public health impact as compared to universal HPV vaccination for men.[32]

Some of the limitations of our study are that it was done among a selective group of men using convenience sampling; hence the findings may not represent the general population. However, it provides valuable information for potential preventive measures and public health campaigns on HPV infection among high-risk men. The survey questions were self-administered hence recall and socially desirable bias could not be excluded.

CONCLUSION

Despite more than a decade of HPV-related infections, our study demonstrates high-risk sexual behaviours and poor knowledge of HPV infection among high-risk men. Engagement in oral sex practice was noted to be almost four times more likely to have adequate knowledge of HPV. Information on HPV infection, its related diseases, and preventive aspects should be made available during STD clinic encounters. It is hoped that the findings of this study can be used as a guide for strategies on HPV education for better awareness and subsequent advocacy for HPV vaccination. This could improve the quality of life for MSM population and HIV-infected men.

ACKNOWLEDGEMENT

We would like to thank the Director General Health Malaysia for his permission to publish this article. The authors would also like to thank Dr Ker Hong Bee and Clinical Research Centre (CRC)Hospital Raja Permaisuri Bainun, Ipoh, for feedback on the questionaire and facilitating data analysis respectively.

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ORIGINAL ARTICLE

Duodenal eosinophilia is associated with symptomatic erosive gastro-oesophageal reflux disease, presence of co-morbidities, and ethnicity but not undifferentiated functional dyspepsia: A retrospective Malaysian study

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ABSTRACT

Background: Duodenal eosinophilia is postulated to play a key role in the pathogenesis of functional dyspepsia, a common condition responsible for considerable impairment of quality of life. Our objective was to evaluate the relative strength of the associations between duodenal eosinophilia, functional dyspepsia, symptomatic erosive gastroesophageal reflux disease (GERD), the presence of co-morbidities, and a number of other variables.

Methods: Eosinophil counts of archived endoscopic duodenal biopsies of 289 subjects were determined by a pathologist blinded to the clinical data. Duodenal eosinophilia was defined by a count of more than 15 per 5 high power fields. Clinical charts were reviewed by a gastroenterologist blinded to the histology review.

Results: In the study sample, the primary diagnosis was functional dyspepsia (undifferentiated by subtypes) in 45, symptomatic erosive GERD in 29, gall stone disease in 17, irritable bowel syndrome in 23, and an alternative or undetermined diagnosis in 175 subjects, respectively. On logistic regression analyses, eosinophil counts were positively associated with symptomatic erosive GERD (Odds Ratio, OR 1.03, 95% Confidence Interval, 95%CI: 1.00, 1.05; p=0.035) but not functional dyspepsia. Pre-defined duodenal eosinophilia was associated with symptomatic erosive gastro-oesophageal reflux disease (OR 3.36, 95%CI 1.18,-9.60; p=0.023), the presence of co-morbidities (OR 2.00, 95%CI 1.10, 3.62; p=0.022), and Chinese (as compared to Malay and Indian) ethnicity but not with either functional dyspepsia, irritable bowel syndrome, gallstone disease, Helicobacter pylori infection, or gender.

Conclusion: Duodenal eosinophilia was associated with symptomatic erosive GERD, the presence of co-morbidities, and Chinese ethnicity but not with undifferentiated functional dyspepsia.

KEYWORDS:
Duodenal eosinophilia, functional dyspepsia, GERD

INTRODUCTION

Functional dyspepsia is a common condition that is responsible for considerable impairment of quality of life.[1] The notion that microinflammation in the duodenum has a key role in the pathogenesis of functional dyspepsia has recently gained much traction.[2] It is postulated that duodenal microinflammation and the accompanying aberration of mucosal permeability are linked to activation of the immune system, visceral hypersensitivity, stimulation of afferent nerve endings, and altered gastroduodenal motor function.[2] Early evidence for this accrued from observations of a subtle increase in duodenal mucosal eosinophil counts in subjects with non-ulcer dyspepsia.[3] The association between duodenal eosinophilia and functional dyspepsia, however has not been uniformly consistent. Some have reported duodenal eosinophilia to be positively associated with functional dyspepsia as a whole[3-5] while others have reported an association with only subtypes of functional dyspepsia[6-9] or indeed no association at all.[10] The relevance of the association between duodenal eosinophilia and functional dyspepsia lies not only in its importance in elucidating the pathogenesis of functional dyspepsia but also in the potential applicability of duodenal eosinophilia as a diagnostic biomarker of functional dyspepsia. The objective of this retrospective study conducted on patients attending a Malaysian hospital was to investigate the strength of the associations between functional dyspepsia, duodenal eosinophilia, and a number of other variables, including age, gender, ethnicity, the presence of co-morbidities, other common gastrointestinal disorders, and *Helicobacter pylori* infection.

MATERIALS AND METHODS

Study Subjects

The study sample consisted of consecutive patients under the care of a single gastroenterologist (SMR) who underwent elective diagnostic oesophago-gastro-duodenoscopy (OGD) in 2019. It was routine practice for a random mucosal biopsy to be taken from the second part of the duodenum for histological examination as well as biopsies from the gastric antrum and body for the detection of *Helicobacter pylori*

This article was accepted: 09 June 2022
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infection by the rapid urease test. Exclusions from routine biopsy included (i) patients in whom the OGD was performed in an emergency setting such as acute upper gastrointestinal bleeding, (ii) patients in whom the indication was primarily therapeutic such as in oesophageal stenting, duodenal stenting, or insertion of percutaneous endoscopic gastrostomy tubes, (iii) patients with a bleeding tendency, and (iv) patients on anti-platelet and/or anticoagulant drugs. A total of 464 patients underwent OGD during the study period and biopsies were taken from 289 subjects who constituted the study sample.

Histological Protocol

The duodenal biopsies of the 289 subjects were retrieved from the archives of the histopathology department and reviewed by a single pathologist who was blinded to the clinical information of the patients. All endoscopic duodenal biopsies in the study hospital were handled, processed, and examined using a standard protocol. The biopsy specimens were mounted directly from the biopsy forceps onto filter paper mucosal surface up and placed immediately in formalin preservative. After overnight processing, the tissue specimens were carefully embedded on edge, perpendicular to the mucosal surface, and sectioned at 3-micron thickness. Six sections were obtained after step sectioning and stained with haematoxylin and eosin. The number of eosinophils was counted in five random high-power fields (HPF) at ×40 magnification and field diameter of 0.55mm. Duodenal eosinophilia was defined as an eosinophil count of more than 15 per 5 (HPF) as proposed by Chaudhari et al.[11]

Clinical chart review and definition of diagnostic groups:

The clinical chart of each patient was reviewed by a gastroenterologist who was blinded to the results of the histology review. The information retrieved from the clinical charts included demographic details, the primary diagnosis, the presence of significant co-morbidities, and the presence of symptoms of anxiety or depression. The definition of significant co-morbidities included but was not confined to conditions such as diabetes, cardiac disease, respiratory disease, chronic kidney and liver disease, malignancy, and infection. The diagnosis of functional dyspepsia was made if the broad criteria of the Rome 4 classification were met including chronicity of upper abdominal symptoms, normal OGDS findings, absence of *Helicobacter pylori* infection, and no other obvious explanation for the symptoms.[12] Based on clinical and investigational findings, three other gastrointestinal disorders that permitted diagnosis with a high level of confidence included irritable bowel syndrome (IBS), symptomatic erosive gastro-oesophageal reflux disease (GERD), and gallstone disease. The diagnosis of IBS was based on the broad criteria of the Rome 4 classification.[12] Symptomatic erosive GERD was defined by the presence of convincing GERD symptoms and endoscopically identifiable erosive changes. Gall stone disease was defined by the presence of gall stones and clinical features that were convincingly attributable to the gall stones. Where symptoms overlapped, the primary diagnosis assigned to the subject was determined by which of the conditions was responsible for the predominant symptoms. When making direct comparisons of the eosinophil counts and rate of duodenal eosinophilia between groups, the IBS group was utilised as the control based on the findings of a previous study that duodenal eosinophilia was not a feature of IBS.[13]

Statistical methods

The Epi InfoTM version 7.2 statistical software package available from the Centres for Disease Control and Prevention (CDC) website was used in the statistical analyses. Differences in the rate of categorical variables between groups were tested by the chi-square test while differences in numerical variables were tested using the non-parametric Kruskal–Wallis test. Logistic regression analysis was used to examine the independent association between multiple explanatory variables and a dichotomous response variable. Association was expressed in terms of odds ratio (OR) and 95% confidence intervals (95%CI). All 289 subjects were included in the logistic regression analyses.

This retrospective study was approved by the hospital research and ethics committee and was conducted in accordance with the ethical standards laid down by the 1964 Helsinki Declaration.

RESULTS

Characteristics of the sample

Female subjects constituted 52.6% (152/289) of the sample. The median age of the sample was 48 years (range 15-88 years). Two hundred and forty (83.0%) of the subjects were Malaysian nationals, 3 subjects did not state their nationality while the remaining subjects were nationals of 24 different countries. In terms of ethnicity, the three largest groups consisted of Indians (n=102), Chinese (n=93), and Malays (n=56). Fourteen of the 102 ethnic Indians and 3 of the 93 ethnic Chinese were not Malaysian nationals.

The primary diagnosis was functional dyspepsia in 45 patients, symptomatic erosive GERD in 29 patients, gallstone disease in 17 patients, and IBS in 23 patients, respectively. The remaining 175 subjects consisted of patients with another primary diagnosis or in whom the primary diagnosis was undetermined. Twenty-seven patients were positive for *Helicobacter pylori* infection and 105 patients had significant co-morbidities. The demographic characteristics, the frequency of co-morbidities, the Helicobacter pylori infection rates, the rates of duodenal eosinophilia (as defined by a count of >15 per 5 HPF), and the absolute duodenal eosinophil counts in the various diagnostic groups are summarised in Table I. Comparison of the three diagnostic groups of functional dyspepsia, symptomatic erosive GERD, and gall stone disease, respectively, with the group of subjects with IBS (that served as a control) revealed that patients with symptomatic erosive GERD were significantly older and more likely to be male than patients with IBS (Table I). There was no statistically significant difference in these parameters between the functional dyspepsia and gall stone disease groups, respectively, and the control group of IBS subjects.

Comparison of eosinophil counts and rate of eosinophilia (>15 counts per HPF) between the diagnostic groups

The rate of eosinophilia as defined by >15 counts per HPF was significantly higher in the group with symptomatic erosive GERD than the IBS group (24/29 vs. 12/23, p=0.018, Table I).

Table I: Demographic characteristics, duodenal eosinophil counts, rates of H pylori infection and rates of co-morbidities in the diagnostic groups

Diagnostic group	Age in years	Gender: females n (%)	Ethnicity: n (%)	Co-morbidities n (%)	H. pylori infection n (%)	Duodenal eosinophilia[a] n (%)	Duodenal eosinophil count (per 5 high-power fields)
Functional dyspepsia (n=45)	39 (24-77)	34 (75.6)	Malay: 6 (13.3) Chinese: 14 (31.1) Indian: 18 (40.0) Other: 7 (15.6)	11 (24.4)	0 (0.0)	23 (51.1)	16 (3-58)
Symptomatic erosive GERD (n=29)	57 (26-88) *	13 (44.8) *	Malay: 7 (24.1): Chinese: 6 (20.7) Indian: 13 (44.8) Other: 3 (10.3)	16 (55.2)	2 (6.9)	2 (6.9)	20 (7-85) **
Gall stone disease (n=17)	47 (29-63)	12 (70.6)	Malay: 4 (23.5) Chinese: 6 (35.3) Indian: 5 (29.4) Other: 2 (11.8)	5 (29.4)	0 (0.0)	11 (64.7)	23 (5-55)
Irritable bowel syndrome (n=23)	44 (25-73)	18 (78.3)	Malay: 3 (13.0) Chinese: 9 (39.1) Indian: 6 (26.1)	7 (30.4)	0 (0.0)	12 (52.2)	18 (2-54)
Other or undetermined diagnoses (n=175)	50 (15-81)	75 (42.9)	Malay: 36 (20.6) Chinese: 58 (33.1) Indian: 60 (34.3) Other: 21 (12.0)	66 (37.7)	25 (14.3)	107 (61.1)	18 (1-75)

Data expressed as median (range) or n (%).
a Eosinophilia defined by a count >15 eosinophils per 5 high power fields.
*Significantly different compared to the irritable bowel syndrome group, *p<0.05.
** Significantly different compared to the irritable bowel syndrome group, p=0.052.

Table II: Logistic regression model of predictors of functional dyspepsia

	Odds ratio (95% confidence interval)	p value
Age	0.97 (0.95-1.00)	0.066
Female gender	3.22 (1.52-6.82)	0.002
Ethnicity: Chinese compared to Malay	1.50 (0.51-4.42)	0.461
Chinese compared to Indian	0.86 (0.39-1.93)	0.724
Chinese compared to Other	0.69 (0.24-2.00)	0.496
Presence of co-morbidities	0.82 (0.35-1.89)	0.635
Duodenal eosinophil count	1.00 (0.98-1.02)	0.878
Symptoms of anxiety or depression	2.38 (1.04-5.46)	0.041

Table III: Logistic regression model of predictors of symptomatic erosive GERD

	Odds ratio (95% confidence interval)	p value
Age	1.02 (0.99-1.06)	0.140
Female gender	0.85 (0.38-1.91)	0.699
Ethnicity: Chinese compared to Malay	0.37 (0.11-1.26)	0.111
Chinese compared to Indian	0.44 (0.15-1.24)	0.119
Chinese compared to Other	0.68 (0.16-2.98)	0.608
Presence of co-morbidities	1.46 (0.60-3.55)	0.400
Duodenal eosinophil count	1.03 (1.00-1.05)	0.035
Symptoms of anxiety or depression	0.41(0.09-1.84)	0.245

Table IV: Logistic regression model of predictors of duodenal eosinophilia (as defined by >15 cells per 5 high power fields)

	Odds ratio (95% confidence interval)	p value
Age	0.98 (0.96-1.00)	0.054
Female gender	0.83 (0.49-1.40)	0.484
Ethnicity: Chinese compared to Malay	3.17 (1.49-6.80)	0.003
Chinese compared to Indian	2.10 (1.14-4.01)	0.018
Chinese compared to Other	1.80 (0.80-4.07)	0.158
Presence of co-morbidities	2.00 (1.10-3.62)	0.022
Helicobacter pylori infection	0.73 (0.31-1.74)	0.484
Functional dyspepsia	0.66 (0.311– 1.41)	0.285
Irritable bowel syndrome	0.60 (0.23-1.53)	0.283
Gall stone disease	1.19 (0.40-3.53)	0.755
Symptomatic erosive GERD	3.36 (1.18-9.60)	0.023

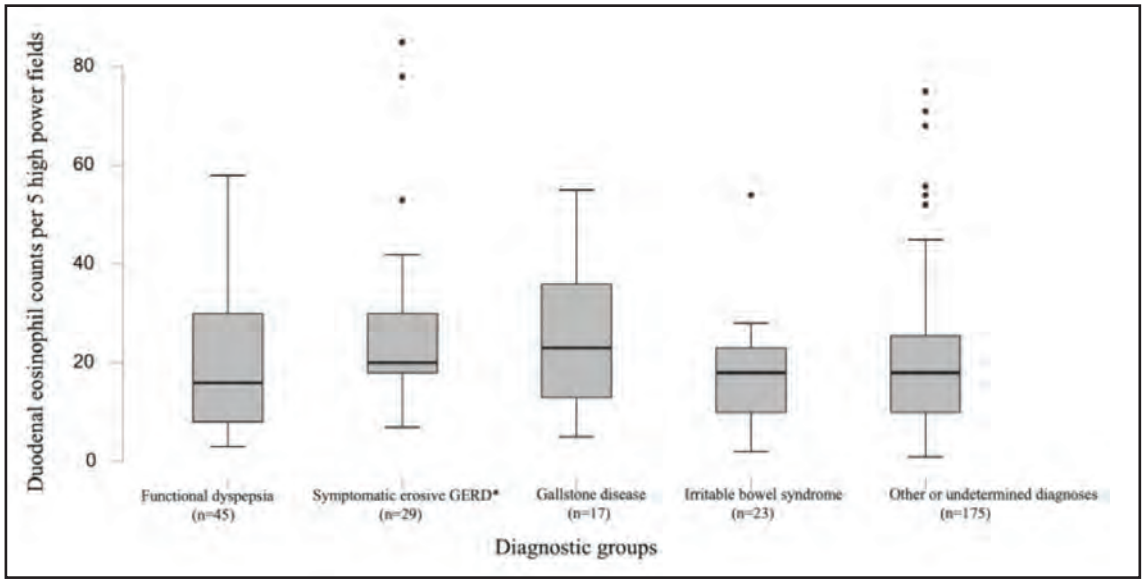

Fig. 1: Distribution of duodenal eosinophil counts in the diagnostic groups

The rates of eosinophilia in the functional dyspepsia and gall stone disease groups were not statistically significantly different from that of the IBS group (Table I). The distribution of the duodenal eosinophil counts in the diagnostic groups is shown in Figure 1. Comparison of the eosinophil counts of the functional dyspepsia, symptomatic erosive GERD, and gall stone disease groups, respectively, with that of the IBS group showed a difference that approached statistical difference only in the case of symptomatic erosive GERD group (Table I).

Logistic regression analyses

Logistic regression analysis with functional dyspepsia as the response variable revealed that functional dyspepsia was significantly predicted by female gender and the presence of symptoms of anxiety or depression but not by elevated duodenal eosinophil counts (Table II). Similar logistic regression analysis with symptomatic erosive GERD as the response variable revealed that symptomatic erosive GERD was independently associated with elevated duodenal eosinophil counts but not with any of the other variables (Table III). Logistic regression analysis with duodenal eosinophilia (>15 counts per HPF) as the response variable showed that duodenal eosinophilia was significantly predicted by the presence of co-morbidities and symptomatic erosive GERD but not by functional dyspepsia or *Helicobacter pylori* infection (Table IV). Duodenal eosinophilia was also associated with Chinese ethnicity as opposed to Malay or Indian ethnicity (Table IV).

DISCUSSION

The key finding of our study was that duodenal eosinophilia was independently associated with symptomatic erosive GERD and the presence of co-morbidities but not with undifferentiated functional dyspepsia. The relationship between symptomatic GERD and increased eosinophils in the duodenal mucosa was evident on two measures; the rate of duodenal eosinophilia (as defined by >15 counts per HPF) and the absolute duodenal eosinophil counts. In contrast, there was no detectable relationship between functional dyspepsia and eosinophils in the duodenal mucosa based on either of the two measures. In this context, it should be noted that normal ranges for duodenal eosinophil counts among healthy adults have not been clearly established. The cut-off value of eosinophils per HPF used to define duodenal eosinophilia in previous publications has been variable, ranging from 15 to 63 per HPF.[4,6,8,11] The arbitrary choice of 15 per HPF in our study as proposed by Chaudhari et al.,[11] was based on the premise that the degree of eosinophilia in conditions such as functional dyspepsia and GERD is likely to be subtle and a relatively lower cut-off would have greater sensitivity in detecting a positive signal. A number of studies have used a cut-off value of >22 counts per 5 HPF to define eosinophilia.[3,4,6] When we reanalysed our data using a cut-off value of >22 counts per 5 HPF, the association between duodenal eosinophilia and concomitant co-morbidities was preserved but the associations with symptomatic erosive GERD, ethnicity, and age were no longer detectable (data not shown).

The failure to find a relationship between functional dyspepsia and duodenal eosinophilic infiltration irrespective of whether it was measured in terms of absolute counts or rate of pre-defined eosinophilia is concordant with the findings of some studies[8-10] but not with others.[3-5] We are cognisant however of a limitation of our retrospective study that restricts the conclusions that can be drawn with regard to the relationship between duodenal eosinophilia and functional dyspepsia. This relates to the fact that while the diagnosis of functional dyspepsia per se was determined with a high level of confidence, the retrospective nature of the study precluded the precision needed to divide the group into the subtypes of epigastric pain syndrome and post-prandial distress syndrome, respectively, as prescribed by the Rome 4 classification.[12] In previous studies, duodenal eosinophilia was most frequently associated with the subtypes of patients with post-prandial distress and early satiety although it has

to be noted that even then the association with these two sets of symptoms was not consistent.[6-9] It may be that the number of subjects with post-prandial distress syndrome in our sample was small and our study was therefore not sufficiently powered to detect an association. Furthermore, in at least one other study, functional dyspepsia was not associated with total duodenal eosinophil counts but was positively associated with eosinophilic degranulation, the latter being a marker of eosinophil activation8. Hence, the absence of an association between functional dyspepsia and duodenal eosinophil counts in our study does not necessarily negate the role of duodenal eosinophils in the pathogenesis of functional dyspepsia.

The finding in our study of an independent association between symptomatic erosive GERD and elevated duodenal eosinophil counts is intriguing. The diagnosis of symptomatic GERD in our study was relatively robust as it was made on the basis of unequivocal endoscopic findings and compatible symptoms. This observation resonates with the findings of a recent study that duodenal eosinophilia in patients with functional dyspepsia predicted the development of GERD 10 years later.[14] The authors of that study postulate that subsets of GERD and functional dyspepsia may be part of the same disease spectrum and that duodenal eosinophilia could well be the link. Our finding lends credence to this hypothesis. Distinguishing with precision between the subtypes of functional dyspepsia and GERD on the basis of the history even with validated questionnaires can be challenging. It is quite conceivable that there is an overlap between patients with symptomatic erosive GERD in our study and subsets of patients with functional dyspepsia. The possibility that this explains the association between duodenal eosinophilia and patients labelled as symptomatic erosive GERD cannot be excluded.

Assigning subjects to the diagnostic groups in our study was predicated on the ability to make the diagnosis with a high degree of certainty from the available information. A substantial number of patients in our cohort would have had non-erosive GERD but we did not assign these subjects to a defined diagnostic group because of difficulties in distinguishing true non-erosive GERD from functional oesophageal disorders in the absence of routine ambulatory pH or impedance testing.

The independent association observed between the presence of co-morbidities and duodenal eosinophilia in our study is perhaps not surprising as there already exists a body of evidence linking systemic illness, abnormal intestinal permeability, and impaired intestinal barrier function.[15] The definition of significant co-morbidities was necessarily broad and included a multitude of illnesses as we wanted to investigate the relative impact of these conditions on duodenal eosinophil counts in comparison to the putative effect of functional dyspepsia.

Another notable observation of our study was that Chinese ethnicity was a more significant predictor of duodenal eosinophilia than Indian or Malay ethnicity. We are unaware of any other study that detected ethnic differences in duodenal mucosal eosinophil counts. The ethnic composition of our sample is not representative of that of Malaysia as a whole and is more a reflection of the local demography, health care seeking behaviour, and referral patterns. This does not however invalidate our observations of the observed association between ethnicity and duodenal eosinophilia. The quantifying of duodenal eosinophils on histological examination does not require sophisticated technology and has potential as a widely available marker of subsets of functional dyspepsia. However, our observation of the possible influence of co-morbidities, ethnicity, and even age on duodenal eosinophil counts suggests that the utility of duodenal eosinophilia alone as a diagnostic biomarker of functional dyspepsia is likely to be limited.

The fact that female gender and symptoms of anxiety or depression independently predicted the diagnosis of functional dyspepsia is consistent with the general experience and suggests that the population of patients with functional dyspepsia attending our institution is unlikely to be substantially different from that of other populations.[1]

An inherent limitation of a retrospective observational study such as ours is the absence of matched healthy controls. We mitigated this weakness in two ways. Firstly, by using the subset of patients with IBS as a compromise control group based on a previous report that duodenal eosinophilia was not a feature of IBS and secondly by using logistic regression analysis to adjust as far as was possible for confounding factors.[13] Another limitation relates to the sample size that is particularly relevant to the gall stone disease group that may not have been sufficiently powered to detect an association with duodenal eosinophilia. Other limitations include the inability to exclude eosinophilic oesophagitis in the absence of oesophageal biopsies and the inability to evaluate the impact of allergies as data on allergies was sketchy. It has been suggested that proton pump inhibitors suppress duodenal eosinophilia.[16] We did not specifically gather data on proton pump inhibitor usage among the subjects in our sample and can only speculate on whether this might have been a factor in not being able to detect an association between functional dyspepsia and duodenal eosinophilia. However, we have no reason to believe that proton pump inhibitor usage is lower in subjects with symptomatic erosive GERD than in functional dyspepsia patients.

CONCLUSION

In conclusion, duodenal eosinophilia in our study was associated with symptomatic erosive GERD, the presence of co-morbidities, and Chinese ethnicity but not with undifferentiated functional dyspepsia. Taken in conjunction with the results of other studies, our findings lend support to the hypothesis that subsets of GERD and functional dyspepsia may be part of the same disease spectrum of which duodenal eosinophilia is a common characteristic.

ACKNOWLEDGEMENTS

We thank the hospital records department of Pantai Hospital Kuala Lumpur for assistance in retrieving the clinical records and Pantai Premier Laboratory for retrieving the archived histology slides.

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ORIGINAL ARTICLE

Treatment of severe coronary artery calcification with intravascular lithotripsy: Initial experience of a prospective single centre registry

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ABSTRACT

Introduction: Coronary artery calcification can lead to suboptimal results when performing coronary angioplasty with conventional techniques. Shockwave intravascular lithotripsy (IVL) has recently been introduced as a new modality to treat heavily calcified coronary arteries. The purpose of this study was to determine the procedural success and safety of IVL in calcified lesions.

Materials and Methods: This was a prospective single-centre study regarding the utility of IVL in treatment of calcified coronary arteries. Intravascular ultrasound (IVUS) was used in all cases to characterise the lesions pre procedure and to assess procedural success post procedure. The primary end point was procedural success, defined by IVL treatment and successful stent implantation. The secondary end point was in-hospital and 30-day major adverse cardiovascular event (MACE).

Results: Five patients with severely calcified lesions were successfully treated with IVL. The primary end point was achieved in all patients. All of the lesions were severely calcified with concentric calcium. Multiple calcium fractures were identified on IVUS after IVL in all cases. None of the patients suffered in-hospital or 30-day MACE. The average diameter stenosis at baseline was 1.8±0.4mm and the post PCI diameter stenosis was 2.9±0.1mm, with significant acute luminal gain of 1.2±0.3mm (p<0.01). There were no complications of coronary dissection, slow or no reflow, stent thrombosis, or vessel perforation.

Conclusion: Our initial experience demonstrates the feasibility and safety of IVL in the management of calcified coronary stenosis. The shockwave IVL is an effective treatment approach to disrupt coronary calcification, facilitating stent implantation with optimal results. It is a safe procedure with a good success rate and low rate of complications.

KEYWORDS:
Intravascular lithotripsy, Intravascular ultrasound, Coronary atherectomy

INTRODUCTION

Coronary artery calcification is due to deposited calcium in the intimal and medial layers of the arterial wall, commonly due to increasing age and co-morbidities.[1] Heavily calcified plaques in coronary arteries are a risk factor for major adverse cardiac events and mortality.[2] Percutaneous coronary intervention (PCI) in calcified coronary arteries is challenging as it may be resistant to dilatation of the calcified segment with angioplasty balloons.[3] During angioplasty, inadequate stent expansion may lead to malapposition of stent struts[4] and subsequently stent thrombosis and early stent restenosis.[5] Coronary calcium can often be treated successfully with different therapeutic calcium debulking techniques, including orbital or rotational atherectomy, excimer lasers as well as cutting and scoring balloons.[6] Non-compliant (NC) balloons may require high pressure for vessel dilation, and the use of cutting balloons in severely calcified lesions can be associated with serious complications such as coronary artery dissection and perforation.[7] There has thus been a need for alternative treatment modalities, especially those which are associated with a minimal degree of complications.

Shockwave intravascular lithotripsy (IVL), a technique similar to the one used in nephrolithiasis, has evolved as a new modality to treat heavily calcified coronary arteries. IVL involves using a percutaneous device to produce acoustic pressure waves resulting in the delivery of sufficient energy to break up superficial and deep calcium deposits.[8] Early studies showed that IVL has been used successfully to treat coronary calcific plaques with minimal vascular complications.[9] Intravascular ultrasound (IVUS) or optical coherent tomography (OCT) are often performed pre-IVL treatment to evaluate the extent of calcification and post procedure as well as to demonstrate calcium fractures and evaluate procedural success.

In this study, we describe the data of a prospective registry in a single centre for the use of IVL to treat severely calcified coronary artery lesions.

MATERIALS AND METHODS

Patients and study design

The Prospective Registry of Calcified Coronary Artery lesions

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Table I: Baseline characteristics

Male, n (%)	5 (100)
Age (mean±SD %)	60±12
Hypertension, n (%)	3 (60)
Hypercholesterolaemia, n (%)	4 (80)
Smoking, n (%)	1 (20)
Family history of cardiac disease, n (%)	3 (60)
Diabetes mellitus, n (%)	1 (20)
LVEF (mean±SD %)	61±1.6
eGFR (ml/min/1.73 m2)	81±25.5
Stable angina / positive stress test	3 (60)
Unstable angina	2 (40)
Male, n (%)	5 (100)

Table II: Procedural characteristics and Clinical Outcomes

Vessel treated	
LAD, n (%)	4 (80)
LCX, n (%)	1 (20)
RCA, n (%)	0 (0)
Lesion characteristics	
Proximal, n (%)	5 (100)
Mid, n (%)	2 (40)
Length (mean±SD), mm	20.6±3.7
Severe calcification, n (%)	5 (100)
Procedural characteristics	
Procedural time (mean±SD)	135.2±13.9
Fluoroscopy time (mean±SD)	28.6±6.5
Femoral vascular access, n (%)	4 (80)
Radial vascular access, n (%)	1 (20)
Number of lithotripsy pulses applied (median, range)	50 (30-60)
Diameter of lithotripsy balloon (2.5 mm), n	3 (60)
Diameter of lithotripsy balloon (3.0 mm), n	2 (40)
Largest diameter of predilatation balloon, mm (median, range)	3.0 (2.5-3.0)
Mean pressure of predilatation, atm (mean±SD)	11.2±1.8
Largest diameter of postdilatation balloon, mm (median, range)	3.0 (2.75-3.25)
Mean pressure, of postdilatation, atm (mean±SD)	14.8±4.6
2 stents/lesion, n (%)	3 (60)
1 stent /lesion, n (%)	2 (4)
IVUS Characteristics	
Baseline MLD (mm±SD)	1.8±0.4
Post PCI MLD (mm ±SD)	2.9±0.1
Baseline MLA (mm2 ±SD)	3.3±0.9
Post PCI MLA (mm2 ±SD)	6.7±0.5
Post PCI Luminal Gain (mm±SD)	1.2±0.3
Angiographic and clinical outcomes	
Procedure success with facilitated stent delivery	5 (100)
Perforation, dissection, slow flow, stent thrombosis	0 (0)
In-hospital MACE (MI/TVR/Death)	0 (0)
30-day MACE (MI/TVR/Death)	0 (0)

is a single-centre study. Approval for the study was granted by Independent Ethics Committee of Ramsay Sime Darby Healthcare. Anonymised data were collected by medical record review and all patients gave written informed consent for inclusion into the registry. Baseline characteristics of patients including age, cardiac risk factors, and clinical presentation were documented from clinical records. Left ventricular ejection fraction (LVEF) and baseline renal function (eGFR) were documented.

Percutaneous coronary intervention

All patients were given dual-antiplatelet therapy and received intra-arterial heparin for anticoagulation during the PCI procedure. Patients underwent IVL with the Shockwave C2 lithotripsy (Shockwave Medical, Santa Clara, CA, USA). IVUS was used in all cases to characterise the lesions pre procedure, and calcium was defined as a (hyperechoic) lesion with a brighter shadow than reference adventitia.10 Measurements of pre and post-PCI mean luminal diameter (MLD) and mean luminal area (MLA) were recorded. The angioplasty balloon size was selected based on vessel diameter measured by IVUS at a 1:1 ratio. The balloon catheter was inflated to 4 atm and up to 10 impulses were delivered at 1 pulse/second. A maximum of up to 80 impulses could be delivered with a single IVL catheter. IVUS was used after IVL to assess procedural success and document procedural complications post procedure. Post-IVL calcium fracture was identified on IVUS as the presence of a new disruption or discontinuity in the calcium arc. Following PCI, all patients were given dual antiplatelet therapy with either

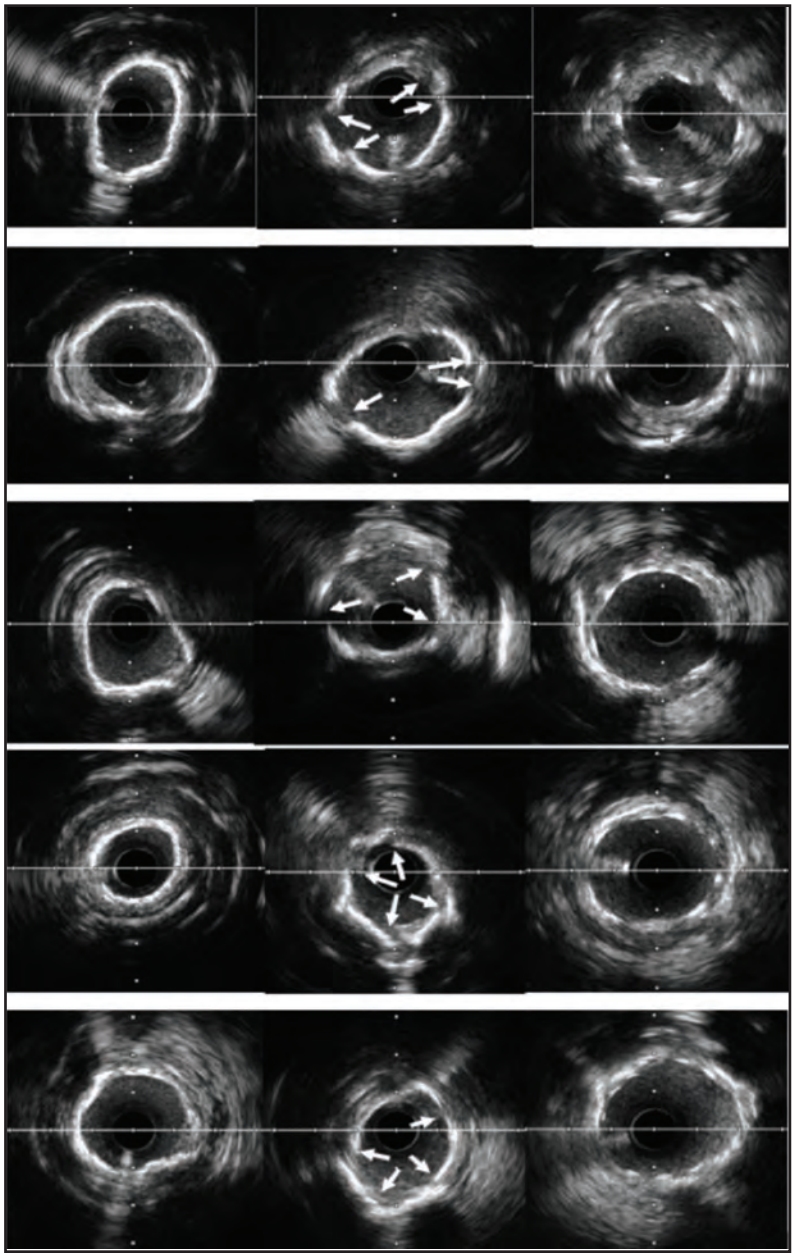

Fig. 1: IVUS images show surrounding severe calcification with concentric arc (left) in all five cases (top to bottom). Corresponding post IVL and calcium fractures (arrows) in the vessel (middle). IVUS images post stenting (right) showing well-apposed stent struts

aspirin 100 mg, clopidogrel 75mg or ticagrelor 180mg/day for 12 months.

Endpoints

The primary end point was procedural success defined as successful IVL treatment and stent implantation with <30% residual stenosis. The secondary endpoint was in-hospital major adverse cardiovascular event (MACE), including cardiac death, myocardial infarction (MI), or target-vessel revascularisation (TVR) and 30-day MACE.[11] Safety outcome was procedural complication, defined as coronary dissection, slow or no reflow, stent thrombus, or vessel perforation.

Statistical analysis

Descriptive statistics, including mean, median, and ranges were used. Categorical variables are presented as counts (%) and continuous variables are presented as mean±standard deviation. The paired t-test was used for comparison of MLD at baseline and after PCI. A $p \leq 0.05$ was considered significant.

RESULTS

Baseline clinical and procedural characteristics.

Between March 2021 and February 2022, five patients with severely calcified lesions were treated with IVL. The baseline characteristics of the patients are shown in Table 1. Mean age was 60±12 years, with a high prevalence of risk factors of hypertension, hypercholesterolemia, and family history of cardiac disease. One (20%) patient had diabetes mellitus (commonly associated with coronary artery calcification).[12]

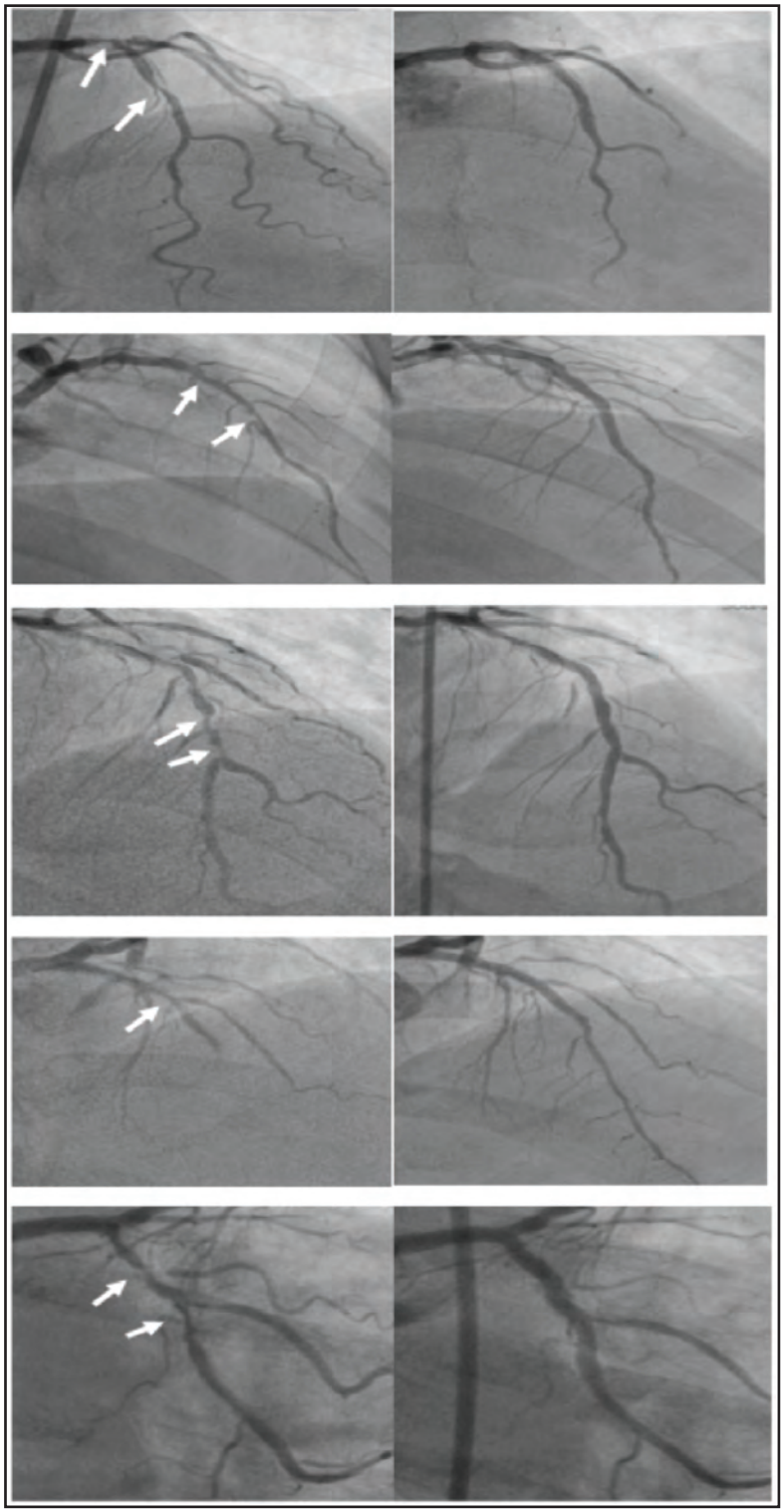

Fig. 2: Pre-procedure angiogram (left) showing areas of calcified stenosis (arrow) for the five patients (top to bottom). Post procedure and corresponding final result after IVL and stenting of the lesion (right)

Procedural characteristics

The procedural characteristics are shown in Table II. Femoral vascular access was preferred in majority of cases. The target artery was the left anterior descending coronary artery in four patients and the left circumflex coronary artery in one patient. All of the lesions were severely calcified, with a mean length of 20.6±3.7 mm, and concentric calcium was present in all lesions. Three IVL balloons of 2.5 mm diameter and two balloons of 3.0 diameter were used. Multiple (≥2) calcium fractures were identified in all five cases after IVL treatment. Pre and Post PCI IVUS images for all cases are shown in Figure 1. In one case, the IVL balloon ruptured during the

Fig. 3: An illustration of the IVL balloon emitting sonic pressure waves.[17]

procedure (after delivery of 30 Shockwave pulses) with no adverse complications. The pre-procedure angiographic images and post-procedure images for all cases are highlighted in Figure 2.

Clinical outcomes

The primary endpoint of procedural success was achieved in all patients. There were no in-hospital MACE and 30-day MACE events (Table 2). The average diameter stenosis at baseline was 1.8±0.4 mm and the post PCI diameter stenosis was 2.9±0.1 mm, with a significant acute luminal gain of 1.2±0.3 mm ($p<0.01$). There were no cases of coronary dissection, slow or no reflow, stent thrombus, or vessel perforation.

DISCUSSION

This study is the first IVL registry to be published from Malaysia. The main findings of our study are as follows: IVL was performed with successful stent delivery in all cases. IVL was safe, with no major angiographic complications and none of the patients had in-hospital and 30-day follow-up MACE.

IVL was first used in Malaysia in Mar 2021.[13] It is a semi-compliant balloon-catheter system integrated with multiple lithotripsy emitters (Figure 3), which transduces electric pulses into sonic pressure waves.[14] The catheter is compatible with 0.014" coronary guidewires and is available in 2.5, 3.0, 3.5, and 4.0mm diameters with a balloon length of 12mm. The treatment is delivered by placing the balloon catheter within the coronary artery at the site of stenosis and inflating it up to 4 atm pressure.[15] The presence of saline and contrast within the IVL balloon facilitates the transfer of pressure waves through the soft tissue into the calcium deposits. The mechanism of calcific plaque modification by IVL includes splitting of calcific plaque by the impact of compressive circumferential forces which are induced by shock waves. There is also the development of microfractures and also macrofractures following cumulative impact of repetitive shock wave pulses.[16]

During delivery of shockwave cycles, electric signals that mimic pacing spikes may be seen on the electrocardiogram trace, possibly due to piezoelectricity (electric charge that accumulates in soft tissue in response to sonic pressure waves).18 Since severe calcification is an important predictor of restenosis after PCI, treatment with IVL can potentially increase the vessel diameter and ensure better stent placement. This reduces the risk of stent under expansion which in turn reduces the risk of stent thrombosis and restenosis.[19] The system also offers potential benefits to treat both superficial and deep calcium with less risk of atheromatous embolisation and reduced vessel trauma with lower balloon pressures. The rare procedural complications of IVL may include slow coronary blood flow, lack of reflow, distal embolisation, coronary artery perforation, and arterial dissection.

Trial Evidence for IVL

The Disrupt Coronary Artery Disease (Disrupt CAD) I and II trials demonstrated the initial safety and feasibility of IVL in calcified coronary lesions.[9,20] The first multicentre prospective study, Disrupt CAD I, enrolled 60 patients with severely calcified vessels and demonstrated successful stent implantation following IVL in all patients. The second trial, Disrupt CAD II, studied 120 cases with extensive coronary artery calcification and showed similarly successful delivery and use of the IVL catheter in all patients. The trial reported no complications of abrupt vessel closure, slow flow/no-reflow, or coronary perforation.

The largest study so far was the Disrupt CAD III study, which was a prospective, single-arm multicentre study including 431 patients with calcified coronary arteries.[21] The primary safety endpoint of the 30-day freedom from major adverse cardiovascular events was 92.2%. There was a high rate of procedural success at 92.4%. OCT demonstrated multiplane and longitudinal calcium fractures after IVL in 67.4% of lesions. This study concluded that IVL had high procedural success in angioplasty of severely calcified lesions with a low complication rate.

STUDY LIMITATIONS

This is a prospective, single-arm registry with a short-term follow-up period of 30 days. The study comprises a small study cohort. Larger randomized studies or clinical registries of IVL with long-term follow-up will be of significant clinical value.

CONCLUSION

Our initial experience demonstrates the feasibility and safety of IVL in the management of calcified coronary stenosis. The shockwave IVL is an effective treatment approach to disrupt coronary calcification, facilitating stent implantation with optimal results. It is a safe procedure with good success rate and low rate of complications.

CONFLICT OF INTEREST

The study did not receive any funding grant. There was no role from any commercial or non-profit sector in the design and interpretation of the study.

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ORIGINAL ARTICLE

Temperature measurement: Must it be the forehead? A prospective cross-sectional study

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ABSTRACT

Background: The aim of this study was to compare temperature readings measured at the forehead and wrist against the tympanic temperature which is generally accepted as the standard.

Method: This is a cross-sectional study carried out on 325 people from the general population entering a private hospital for consultation or work. Forehead and wrist temperature was taken using the CEFC RoHS K3 model (China) and tympanic temperature using the Braun Thermoscan 7 Thermometer Irt6520 by the same investigator on consenting individuals.

Results: There was no significant difference between the forehead (mean =36.6, standard deviation, SD=0.30) and tympanic (mean=36.6, SD=0.41), Z= -1.609, p=0.108. However, there was significant difference between the wrist (mean=36.4, SD= 0.28) and tympanic (mean=36.6, SD=0.41) temperature values, Z= -8.749, p<0.001, the former being lower. Temperature measured at forehead (mean=36.6, SD=0.30) was also significantly higher than the wrist (mean=36.4, SD=0.28), Z= -9.381, p<0.001. The wrist temperature values were lower than forehead and tympanic.

Conclusion: Forehead temperature values are better representatives of the core temperature (tympanic) and be the preferred site of measurement compared to the wrist.

KEYWORDS:
Temperature, wrist, forehead, tympanic, compare

INTRODUCTION

With the current Covid-19 pandemic has come the need to identify and isolate people who are infected and with symptoms, who are a threat to the public. Many measures have been put in place to ensure public safety as advised by the World Health Organization (WHO). It had become a norm early in the pandemic to measure the temperature of individuals who frequent public places for work, daily needs, or recreation as fever was identified as one of the common symptoms of COVID-19 infection.

Temperature can be measured by various means and at various sites on the body and accuracy of readings is important. Studies have looked at the validity of various sites in terms of accuracy and stability.[1,2] Most commonly used are the non-contact infrared thermometers (NCIT) where infrared rays are used to measure heat generated by the body or an object. Research shows that NCITs are accurate, comfortable, and reliable and most importantly fast.[3] However, handheld infrared thermometers have their limitations too and require individual validation.[4,5] Some, however, question the safety of pointing the thermometers at the forehead suggesting that frequent exposure may lead to some health issues in the future. However, there is no concrete evidence to support this. How often does an individual have their temperature taken in a day prior to this pandemic compared to several times in a day during the pandemic? With the various controversies, the public is fearful and unsure, also fearing risks to the pineal gland from frequent exposure to the NCIT despite reassurance about safety of the use.[6] Others are not comfortable with the pistol-like object aimed at humans' forehead possibly evoking a primal terror no matter how benign the instrument may be.[7] There is research suggesting wrist measurement is more stable than forehead measurement while another suggests otherwise.[1,8]

The goal of this study was to determine the differences in temperature values taken at the forehead and inner wrist, the reference (standard) being the temperature of the ear (tympanic membrane). Forehead and wrist temperatures were taken using the infra-red thermometers, CEFC RoHS K3 model (China), and tympanic temperatures using Braun Thermoscan 7 Thermometer Irt6520, respectively, for the purpose of this study with an acceptable difference of ±0.2°C.

MATERIALS AND METHODS

Data were obtained from the routine screening carried out on all patients and staff, respectively, at the entrance of the Negeri Sembilan Chinese Medical Hospital (NSCMH), a private hospital before entering the premises from February to March 2021. Forehead, inner wrist, and tympanic membrane temperatures were taken using a NCIT after informed consent was obtained from participants. The tympanic temperature reading was taken as the standard against which the temperature from other sites was measured. As this was temperature measurement carried out at the entrance of the hospital premise, we were unable to check the ear canal for patency prior to the measurement. Furthermore, these measurements were conducted during the pandemic and unnecessary contact with individuals was prohibited.

Temperatures measurement

Forehead and wrist temperatures were taken using the CEFC

This article was accepted: 13 June 2022
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RoHS K3 model (China) that had an accuracy of ±0.2°C with a temperature range of 10-40oC. The tympanic temperature was measured using the Braun Thermoscan 7 Thermometer Irt6520 which had features like patented pre-warmed tip that was supposed to help ensure professional accuracy of up to 0.2°C. Tympanic thermometers measure the thermal radiation from the tympanic membrane within the ear canal.

The tympanic measurement was taken with disposable sleeves for the probe provided by the manufacturer. Using disposable sleeves, the probe was gently inserted into the external auditory meatus, holding until a beep was heard, and reading was then recorded.

Forehead temperature was taken by approaching the front of the thermometer and within 5–10cm from the forehead as instructed by manufacturer and wrist measurement was taken by holding up the palmar surface of the wrist in the same manner. The thermometers were ensured to be calibrated and stable before use. Temperature measurement technique advised by the manufactures was adhered to during the process of measurement. Device was used out of the box directly after unpacking and already calibrated by the manufacturer. The irt6520-thermoscan infrared ear thermometer is initially calibrated at the time of manufacture and according to the manual, if this thermometer is used according to the use instructions, periodic re-adjustment will not be required. All measurements on consenting individuals were obtained and recorded by the same personnel.

Statistical analysis

Data were collected over a period of two months and later analysed using the IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, USA). Assuming alpha=0.05, beta=0.1 (power 90%), minimum allowable difference of temperature between ear and forehead or wrist = 0.2 degree, standard deviation (SD)=1, we estimated a sample size of 325 (which includes a 20% higher value to account for dropout and errors) participants. Sample size was calculated by the Study Size 2.0.4. Sweden: Cresostat HB, 2017 Software. A normality test was carried out, and since data was found to be not normally distributed, a Wilcoxan Signed Rank test was performed to compare the temperature values.

Ethical clearance was obtained from the National Malaysian Research Registry (NMRR), Ministry of Health Medical Research Ethics Committee (MREC) ID: NMRR-20-2857-56240.

RESULTS

A total 325 individuals participated in the study, 50 % (n=163) were females and 50 % (n=162) males. The participants' age ranged from 13 to 87 with an average age of 46.

We had compared temperatures between:

1. Forehead and wrist
2. Forehead and tympanic
3. Wrist and tympanic.

Kolmogorov-Smirnov test of normality showed that data were not normally distributed, $p<0.05$ for forehead, wrist, and tympanic temperatures, respectively. Therefore, the null hypothesis was rejected and the non-parametric test, Wilcoxon Signed Rank test was carried out.

Forehead and wrist temperature values.

The results showed a difference in temperature values between forehead (mean=36.6, SD=0.30) and wrist (mean=36.4, SD=0.28). A Wilcoxon signed-rank test showed statistically significant difference in temperature readings between forehead and wrist ($Z= -9.381$, $p<0.001$, Table I).

Forehead and tympanic temperature values.

The results showed no difference in temperature values between forehead (mean=36.6, SD=0.30) and tympanic (mean=36.6, SD=0.41). The Wilcoxon signed-rank test showed no statistically significant difference in temperature readings between forehead and wrist ($Z= -1.609$, $p=0.108$, Table I).

Wrist and tympanic temperature values.

The results showed a significant difference between wrist (mean=36.4, SD=0.28) and tympanic temperature values (mean=36.6, SD=0.41). The Wilcoxon signed-rank test showed a statistically significant difference in temperature readings between wrist and tympanic ($Z= -8.749$, $p<0.001$, Table 1).

DISCUSSION

Common symptoms noted in COVID-19 patients are fever, fatigue, and dry cough. Fever was commonly the first presenting symptom. Therefore, temperature screening became the tool used for the high-risk population as well as the general population for the early identification of COVID-19 infection worldwide to reduce the risk of spread.[9] There is a long-term implication in need for early detection, isolation, and management, in terms of lives, economy, and future. Every small measure towards the safety of lives would make a difference.

Non-contact infrared thermometry involves the assessment of skin surface temperature through the measurement of its emitted radiation in the infrared waveband. The use of forehead skin temperature measurement for detection is because blood vessels distribute only about 0.1 mm beneath the forehead skin, making it easy to detect. Using forehead thermometer can eliminate the discomfort and inconvenience caused by the traditional contact thermometer's insertion into the ear, mouth, or rectum.[10] Most of all there is no contact, which eliminates the risk of infection transmission.

Foster et al in their review state that a screening thermograph or spot measurement for the detection of fever should be measured at the face only, but during these pandemic, alternative anatomical locations have been seen to be used (i.e., the wrist). However, these do not comply with international guidelines and are considered too unreliable.[11] They conclude that skin temperature assessment with non-contact infrared thermometry can sufficiently track core body

Table I: Comparing wrist, forehead, and aural temperatures (n=325)

	Mean	Standard deviation	Z	p value
Forehead	36.6	0.30	-9.381	<0.001
Wrist	36.4	0.28		
Forehead	36.6	0.30	-1.609	0.108
Tympanic	36.6	0.41		
Wrist	36.4	0.28	-8.749	<0.001
Tympanic	36.6	0.41		

temperature, but only with appropriate technology and under standardized conditions. They also state that NCIT assessment of either the forehead or inner eye canthus though have the utility for fever screening, cannot replace conventional methods of internal temperature assessment.[11] However, handheld infrared thermometers have their limitations too and require individual validation.[4,5,12]

We looked to compare the temperature values at three different sites, namely the forehead, wrist, and tympanic (standard) on each individual. For this research, we identified tympanic temperature as the reference as all other more accurate sites for core temperature are more invasive. The tympanic temperature has been found to be close to the core temperature of the body and gives the most accurate representation of the body temperature.[8,13]

There was a significant difference in temperature values between the wrist and forehead, wrist, and tympanic. The wrist temperature values were lower than the forehead and tympanic values. Data in febrile humans indicate that core and skin temperature responses vary between participants, environments, and pathogen. Hand skin temperature is likely to decrease during fever development. Data using NCIT for fever screening in children indicate that facial temperatures (i.e., forehead and inner canthus) can provide a good estimate of a raised core temperature under well-controlled conditions.[11]

A study investigating the impact of infrared sensors on core body temperature monitoring by comparing measurement sites found that the measurement values for wrist temperature showed significant offsets with the tympanic temperature and thus cannot be used to screen fevers.[8] Similarly, our data analysis suggested that the forehead reflected the core temperature better than the wrist, with the wrist temperature being significantly lower than the tympanic temperature. Our results also agree with a previous study on the agreement between the core temperature values and the forehead, tympanic membrane, and axillary values in postoperative adult patients in clinical practice that found that forehead temperature recordings showed a good correlation with the core temperature with accuracy that was comparable to the tympanic temperature.[14]

Research by Chen et al that aimed to compare the accuracy of individuals' wrist and forehead temperatures with their tympanic temperature under different circumstances (means of transportation to the hospital: by foot, by bicycle/electric vehicle, by car, or as a passenger in a car) found the wrist temperature to be more stable than the forehead temperature readings. However, they concluded that both measurements have fever screening abilities for indoor patients.[1]

One research where patients' body temperature was measured by four peripheral methods; oral, axillary, tympanic, and forehead along with a standard central nasopharyngeal measurement, found that the tympanic and forehead measurements had the highest and lowest accuracy for measuring body temperature, thus recommending tympanic temperature measurement for patients in ICU.[15] Notably, all these studies had differences in terms of type of population and environments compared to ours.

One research investigated the sensitivity and specificity of two temperature measurement methods – wrist and forehead and compared with the sublingual or axillary standard methods. Researchers found that the wrist and forehead temperatures measurement were not accurate in detecting fever although forehead measurement though not an ideal method, nevertheless appeared more consistent than wrist measurement.[16]

In a summary of evidence on the reliability of one form of temperature checking over another, the authors note that there is currently no gold standard thermometer type, manufacturer, or route. They reviewed several studies and reported that the thermometers that are compared, and accuracy measured also appears to be inconsistently reported across studies including systematic reviews.[17] A systematic review and meta-analysis accuracy of peripheral thermometers for estimating temperature concluded that peripheral thermometers do not have clinically acceptable accuracy and should not be used when accurate measurement of body temperature is required when making clinical decisions.[18] Evidence suggests that they are not acceptable methods for detecting temperatures outside the normothermic range and do not detect fever accurately.[19]

There have been concerns about the accuracy of non-contact handheld infra-red thermometers for measuring temperature during the pandemic. There has been recommendation for the use of infra-red thermal imaging cameras at entrances as they are more accurate with a wider temperature and avoid missing the potential hottest points of the body surface, such as the inner canthus of the eye. They are argued to be more accurate than the handheld infra-red thermometers.[20] However, at our premise and most public establishments, handheld NCIT were commonly used and often individuals tried to use their wrists as an alternative. Awareness regarding inaccuracy of the wrist as opposed to the forehead need to be increased for public to understand the importance and comply.

CONCLUSION

Accuracy of temperature reading is very important especially during this pandemic where there is a need to identify those at high risk so they can be monitored and medically managed hence reducing the spread to the general population. Our results suggest that the forehead temperature reflects the tympanic temperature better than the wrist and thus suggest that wrist temperature not be used interchangeably with the forehead temperature for fear of missing individuals with fever.

LIMITATION

- All temperature measurements were taken at the entrance of the hospital before individuals could enter the hospital building; hence, environmental temperature, effect of air-conditioned cars, and other external factors could not be standardized.
- Weight, height, and body mass index were not taken due to the challenge and policies of social distancing.
- Ear canal patency prior to measurement of temperature could not be performed due to the social distancing policies

There is no conflict of interest among contributors to the conduct of this study.

ACKNOWLEDGEMENT

We would like to thank Dr Sangeetha Shyam M.Sc, PhD. Senior Lecturer, Division of Nutrition and Dietetics, School of Health Sciences, International Medical University for her guidance and contribution during the statistical analysis,

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SHORT COMMUNICATION

Twenty-first century skills teaching in anaesthesia

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SUMMARY

The core competencies defined by the Accreditation Council for Graduate Medical Education merge under the 21st century skills. Technological advancements and globalisation have posed new requirements on all fronts. The 21st century skills are the 12 essential abilities for success in the internet age. Medical education has adapted the 21st century skills in all aspects. The 21st century skills are essential for producing relevant doctors in the age of internet and artificial intelligence. In this article, we present an example of teaching the anaesthesia basics by applying the 21st century skills.

The advancements of the new millennium of the 21st century at all fronts have posed new challenging demands globally. Globalisation and technological advancements have embarked the medical profession. The skills taught in medical schools 20 years back need to be updated as per the latest involvement of the technology in medical profession and globalisation. To keep at par with the globalised world, medical professionals need to possess these 21st century skills.

The 21st century skills are the 12 essential abilities for success in the internet age. These skills (critical thinking, creativity, collaboration, communication, information, media, technology, flexibility, leadership, initiative, productivity, social skills) are grouped under one of the three categories namely, (i). learning skills, (ii). literacy skills, and (iii). life and career skills.[1,2]

The higher education has adapted the 21st century skills in all aspects.[3-5] The six major competencies defined by the Accreditation Council for Graduate Medical Education (ACGME) viz patient care, medical knowledge, professionalism, systems-based practice, practice-based learning and improvement, and interpersonal and communication skills merge under the 21st century skills.[6]

In medical education, these skills are essential for producing relevant doctors in the age of internet and artificial intelligence.

In this article, we present an example of teaching the Mendelson syndrome at undergraduate level, the basic topic in anaesthesia, applying the 21 century skills.

Mandelson's syndrome is the aspiration of gastric contents under anaesthesia.[7] Fasting guidelines and anti-aspiration prophylaxis is a must to prevent the consequences of the syndrome.

Application of 21st Century skills:
The Learning skills include (1) critical thinking, (2) creativity, (3) collaboration, and (4) communication. The four C's, incorporate the mental process required for the modern-day medical professional environment improvement.

Applying the 4 C's:
1. 'Critical thinking' inculcates teaching the 'must know' and the theoretical basis of the Mandelson syndrome.
2. 'Creativity' comes into play in teaching the fasting guidelines taking into consideration the local cuisine of the patient. For example, for the Asian culture, the fried food must be fasted for 8 hours, the milk tea for 6 hours, and clear juice for 2 hours.
3. 'Collaboration' with the other disciplines managing the patient. For example, if the patient is on anti-diabetic management, the medication needs to be held to prevent hypoglycaemia as the patient is fasting. Thus, multidisciplinary collaboration is essential for the individualised care of the patient.
4. 'Communication' with the patient as well as with the relatives to plan the diet do's and don'ts. For example, the caretaker needs to be informed which food should be avoided. At the same time, communication with the other disciplines involved and the nurses who will be taking care and serving anti-aspiration prophylaxis if required is a must.

The Literacy skills include: (1) Information, (2) Media, (3) Technology referred as IMTs. The IMTs equip to discern the facts, the sources of the information, and the technology involved.

Applying the IMTs
1. 'Information Literacy' refers to understanding facts, statistics, figures, and data. For Mandelson syndrome, it refers to the incidence, risk factors, and effectiveness of preventive measures.
2. 'Media Literacy', implies to discern the sources of information available. Practice of evidence-based medicine is emphasised. Various platforms for the understanding of the subject are available, but to choose

This article was accepted: 13 May 2022
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the approved and valid platforms, for example, the Medscape in addition to the textbooks.
3. 'Technology Literacy' refers to understanding the technology involved. For instance, understanding the various types of airway devices and how the endotracheal tube with the inflated cuff prevents Mandelson syndrome.

The 'Life and career skills' encompasses (1) Flexibility, (2) Leadership, (3) Initiative, (4) Productivity, and (5) Social Skills (FLIPS). These relate to personal life joining the professional life.

Appling FLIPS:
1. 'Flexibility' implies understanding the basic concepts, using them in a flexible way individualising to the patient concerned. It may not be possible to follow the strict 2,4,6, and 8 guidelines as patient may not be willing to get up in the night to eat before fasting. Thus, the idea is to mould it according to the patient's eating preferences.
2. 'Leadership' lies in following the concepts of Mandelson syndrome, preaching the principles to all involved and encouraging everyone to follow.
3. 'Initiative' to conduct webinars to educate health care professional as well as the public.
4. 'Productivity' implies moulding the principles in a productive manner. In emergency setting, it may not be possible to follow the fasting guidelines, so providing the anti-aspiration prophylaxis and modifying the anaesthesia accordingly can be a solution.
5. 'Social skills' are essential for health care professionals to deal with patients as well as colleagues. They come into play while dealing with a surgeon colleague and unfasted patient posted for an elective procedure planned under regional anaesthesia block. Here, it is essential to communicate to the patient and the surgeon, the risks involved, and the reason for postponement in a friendly way.

These skills can be incorporated into teaching other subjects as well. It is the need of the hour to equip our medical graduates with these specialised skills to be at par with the ever-advancing world of technology, artificial intelligence, and globalisation.

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Progestogens in the management of miscarriage and preterm birth

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SUMMARY

Miscarriage affects up to 20% of pregnant women, resulting in substantial psychological repercussions in addition to inherent problems from bleeding and infection. Preterm births constitute about 7-12% of all births but are over represented in terms of perinatal morbidity and mortality. Despite existing trials examining the use of progestogens in both these conditions, there is a dearth of guidelines for the practicing clinician. A systematic review of the literature was performed by an expert panel formed by the Obstetrical & Gynaecological Society of Malaysia from the inception of the databases searched up to February 2020, without language restrictions. The level of evidence and recommendations was determined by the panel and peer-reviewed by local and international experts. The use of progestogens is recommended in women with threatened miscarriages who have experienced previous miscarriage as luteal phase support in women undergoing assisted reproduction and in women with short cervix of <25mm in the midtrimester. In addition, it can be considered in women with recurrent miscarriage, where no other cause is identified. This article reviews the existing evidence including the guideline above and is intended to aid primary care doctors and obstetricians in their prescribing practices when managing these common conditions.

KEYWORDS:
Cervical insufficiency, dydrogesterone, luteal phase, preterm labour, progesterone, recurrent miscarriage

KEY CONTENT

- In women with threatened miscarriage, the use of progestogens is associated with a higher incidence of live birth. This benefit is more apparent in the subgroup of women with previous miscarriages.
- Progestogens may be considered in women with unexplained recurrent miscarriages. There is some evidence of a biological gradient, where the benefit appears to increase with the number of previous miscarriages.
- Progestogens are recommended to support the luteal phase in patients undergoing IVF, although there is no clear evidence to indicate the superiority of any particular type of progestogen, their dose, or route of administration.
- Vaginal progesterone should be considered in singleton and twin pregnancies with a short cervix, regardless of history of prior preterm births (PTB). This benefit cannot currently be extrapolated to women with higher order multiple pregnancies.

LEARNING OUTCOMES

- Be able to compare the use of progestogens in various clinical conditions in early pregnancy, incorporating the latest evidence from well-conducted randomised trials
- Be able to recognise that the benefit of progestogens in women with threatened and recurrent miscarriage is dependent on the number of previous miscarriages experienced
- Be able to effectively use progestogens in the prevention of late miscarriage and preterm birth in women with short cervix

PRACTICE GAPS

- Should progesterone be withheld in women with bleeding in early pregnancy unless they have experienced three or more previous miscarriages, as the evidence is more robust in this subgroup of women?
- Should the practice of giving intramuscular 17-α-hydroxy-progesterone caproate be ceased based on the recent data from PROLONG trial?

INTRODUCTION

Miscarriage is defined as pregnancy loss from the time of conception until 24 weeks of gestation. It is considered as one of the most common complications of early pregnancy, affecting up to 20% of pregnant women.[1] In addition to causing excessive bleeding, infection, and other possible complications related to surgical treatment, miscarriages may also give rise to substantial psychological repercussions, including anxiety, depression, and post-traumatic stress disorder.[2] Approximately 50-70% of miscarriages are associated with chromosomal abnormalities in the conceptus, with autosomal trisomy-especially trisomy 16,

This article was accepted: 05 October 2021
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triploidy, and monosomy X being the predominant chromosomal aberrations reported in the first trimester.[3] A smaller, potentially preventable proportion of miscarriages may be caused by luteal phase deficiency, while in the remainder, the cause is not known.

Progestogen is an umbrella term which encompasses progestins (synthetic progestogens) and naturally occurring progestogen such as progesterone. Progesterone is produced by the corpus luteum in the ovary and is required to prime the endometrium for embryonic implantation. Other postulated protective mechanisms of this hormone include modulation of maternal immune response, suppression of the inflammatory response, reduction of uterine contractility, and improvement of utero-placental circulation.[4]

It is this physiological importance that has prompted the utilisation of progesterone supplementation in early pregnancy to prevent miscarriages, largely in three different circumstances; the first, in women who have started to bleed during early pregnancy in an attempt to preserve the pregnancy, while the second, to prevent further loss in asymptomatic women with previous unexplained recurrent miscarriage. Thirdly, progestogen has also been widely used in patients undergoing assisted reproduction.[5] Beyond the first trimester, progestogen has a more established role in the prevention of preterm births, although the evidence is less robust in women with multiple pregnancies.[6-8]

As progestogens are available in various forms, dosages, and indications, it can be a source of confusion for clinicians, especially since there is a dearth of clinical guidance in prescription. This Continuous Medical Education (CME) article was written as a supplement to the guideline produced by the Obstetrical & Gynaecological Society of Malaysia (OGSM) aimed at increasing prescriber confidence amongst general practitioners, family medicine specialists, and obstetricians alike and will primarily focus on formulations available in the country.

METHODOLOGY

A panel of experts in the field of Obstetrics and Gynaecology was appointed by the society to determine clinical knowledge gaps in the management of miscarriage and to formulate a practice guideline. The experts included general obstetricians and gynaecologists, reproductive medicine, and maternal fetal medicine subspecialists from the Ministry of Health Malaysia, local public and private universities, and private practice. A modified Delphi method was used and the panel of eleven experts, including the chairperson who acted as the moderator, determined that the use of progestogens in miscarriage was a key area to address. A second round of discussion specifically identified threatened miscarriage, recurrent miscarriage, and luteal phase support as areas with clinical gaps that require a practice guideline. As miscarriage and birth around the threshold of viability were considered a continuum, this was expanded to include preterm births.

Systematic review of the literature was performed via Medline, Database of Abstract of Reviews of Effects (DARE), Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic reviews and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from its inception until February 2020 without language restrictions. The panel was divided into four groups where each member independently extracted data on the allocated subset of miscarriage or preterm birth and assessed the study quality. The panel determined the level of evidence and recommendations. The guideline was produced and peer-reviewed by local and international experts. Proposed changes were revised and when there was no clear consensus, the opinion of the majority, including the chair, was followed.

THREATENED MISCARRIAGE

A Cochrane review updated in 2018 on the use of progestogen for this specific indication included seven trials involving 696 participants, with low to moderate quality of evidence. The results indicated that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduces the risk of miscarriage; (risk ratio (RR): 0.64; 95% confidence interval (95%CI): 0.47, 0.87; 7 trials; 696 women), while treatment with oral progestogen compared to no treatment also probably reduces the miscarriage rate (RR 0.57, 95%CI: 0.38, 0.85; 3 trials; 408 women). However, treatment with vaginal progesterone compared to placebo, probably has little or no effect in reducing the miscarriage rate (RR: 0.75; 95%CI: 0.47, 1.21; 4 trials; 288 women). The review thus concluded that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduced the risk of miscarriage. However, the use of vaginal progesterone probably had little or no effect when compared with placebo.[9]

By far the largest to date, the recently published Progesterone in Women with Bleeding in early Pregnancy (PRISM) trial was a multicentre, randomised, double-blinded, placebo-controlled trial conducted across 48 hospitals in the UK.[10] A total of 12,862 women were eligible, of which 4153 were randomly assigned to receive either 400 mg of vaginal micronised progesterone (2079 women) or placebo (2074 women) twice daily. The rectal route was an alternative to women whom vaginal administration was unacceptable and notably, this was the preferred route in 1% of women, demonstrating a high acceptability of vaginal progesterone.

The trial showed that among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester of pregnancy did not result in a significantly higher incidence of live births at or beyond 34 weeks of gestation (75% vs. 72%, relative rate 1.03, 95%CI: 1.00, 1.07; p=0.08). However, further subgroup analysis showed that progesterone had possible benefits in women with bleeding in early pregnancy and with a previous history of miscarriage. While live birth is the appropriate primary outcome, there was also no significant difference in the incidence of miscarriage with or without the use of progesterone (20% vs. 22%, relative rate 0.91, 95%CI: 0.81, 1.01). This would be a useful parameter to compare with less-well designed studies looking at miscarriage as the primary outcome. Interestingly, of the 12,862 women who were eligible for randomisation, 8709 or two-thirds of women declined to participate. An economic evaluation subsequent to this, using the same

PRISM cohort, found that progesterone was likely to be a cost-effective intervention in women with a previous miscarriage. Despite an additional £76 per patient in the progesterone arm, the cost-effectiveness acceptability curve for the base-case analysis was favorable. The discordance between clinical and health economic outcomes was attributable to the estimation and quantification of the uncertainty around clinical end-points.[11]

A more recent meta-analysis of 10 randomised controlled trials (RCTs) subsequent to the aforementioned Cochrane review included findings from PRISM and specifically re-examined live birth as the primary outcome. The authors found that progestogens increased the incidence of live birth (RR 1.07, 95%CI: 1.00, 1.15; p=0.04; I2=18%) but the benefit was only seen in with oral progestogen (RR 1.17, 95%CI: 1.04, 1.31; p=0.008; I2=0%) and not in vaginal progestogen (RR 1.04, 95%CI ; 1.00, 1.08; p=0.07; I^2=0%;). Similarly, oral progestogen reduced the risk of miscarriage (RR 0.73, 95%CI: 0.59, 0.92), but not when administered vaginally.[12] A small, open-labelled RCT involving 141 women directly investigated the efficacy of oral micronised progesterone compared to dydrogesterone.[13] The authors did not find any difference in the primary outcome of miscarriage prior to 16 weeks of gestation (10.2% micronised progesterone versus 15.2% dydrogesterone; p=0.581) or resolution of bleeding by days 4-10 (89.7% micronised progesterone versus 96.6% dydrogesterone; p=0.272). Significantly more women on oral micronised progesterone complained of drowsiness and giddiness during treatment.

It is also worth noting that commonly dispensed advice such as bed rest, use of human chorionic gonadotrophin (hCG), or uterine muscle relaxants are not recommended in the management of threatened miscarriage.[14,15]

RECURRENT MISCARRIAGE

American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) defines recurrent miscarriage as two or more consecutive miscarriages.[16,17] We have chosen to adopt the definition proposed by the ASRM and ESHRE as this is well-supported by a large study which found that the likelihood of detecting an abnormality after two losses was similar to that after three or four or more losses.[18] Approximately 0.5-2% of women experience recurrent loss. While there are some well-defined causes of recurrent pregnancy loss, in almost 50% of cases, the aetiology cannot be determined, and is therefore classified as unknown aetiology or unexplained.[19,20] For the purpose of this document, recurrent miscarriage will refer to recurrent pregnancy losses of unknown aetiology.

A 2013 Cochrane review of randomised or quasi-RCTs compared progestogens with placebo or no treatment, given in an attempt to prevent miscarriage.[21] The reviewers found that while there was no evidence to support the routine use of progestogen in early to mid-pregnancy, there appeared to be improved outcomes in women with a history of three pregnancy losses or more to reduce the risk of miscarriage (Peto OR 0.39; 95%CI: 0.21, 0.72, 4 trials; 225 women). It should be noted that the primary outcome was a risk of miscarriage rather than livebirths and the four trials included were of substantial methodological limitations. A more recent Cochrane review then reanalysed data from trials specific to women with recurrent miscarriages and suggested that there may be a reduction in the number of miscarriages in women given progestogen supplementation, compared to placebo or controls (average RR: 0.73, 95%CI: 0.54, 1.00, 10 trials; 1684 women; moderate quality evidence).[22] A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences in rates of miscarriage. Furthermore, there was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate. It was therefore concluded that for women with unexplained recurrent miscarriages, supplementation with progestogen therapy probably reduces the rate of miscarriage in subsequent pregnancies.

One of the trials included in this most recent Cochrane Review was a randomised double-blinded trial involving 388 patients with recurrent pregnancy loss comparing 20 mg dydrogesterone daily to a placebo. The trial demonstrated that the incidence of a further miscarriage was 2.4 times higher in the placebo group (RR: 2.4; 95%CI: 1.3, 5.9), thereby supporting the use of dydrogesterone to improve pregnancy outcomes.[23]

The Progesterone in Recurrent Miscarriages (PROMISE) in 2015 compared micronised progesterone at a dose of 400mg twice daily to vaginal placebo capsules, soon after a positive urinary pregnancy test (and no later than 6 weeks gestation) until 12 completed weeks, with the primary outcome being live birth after 24 weeks of gestation.[24] A total of 836 women who conceived naturally within one year were randomised. In an intention-to-treat analysis, the rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group (RR: 1.04; 95%CI: 0.94, 1.15; rate difference: 2.5 percentage points; 95%CI: -4.0, 9.0). There were also no significant inter-group differences in the rate of adverse events including the incidence of congenital anomalies and specifically genital anomalies. Based on this finding, ESHRE guideline concluded that vaginal progesterone in early pregnancy was of no benefit in women with unexplained recurrent pregnancy loss. However, it acknowledged that there was some evidence of efficacy when oral dydrogesterone was initiated at the time of confirmation of fetal heart activity.[17]

Another recent systematic review and meta-analyses included 21 RCTs that assessed a myriad of therapeutic options in recurrent pregnancy loss and concluded that treatment with progestogens starting in the luteal phase seemed effective in increasing live birth rate but not when started after conception.[25] No head-to-head RCT has been conducted specifically to compare the various progesterone options, doses, or the modes of administration.

In May 2019, the findings of the PRISM trial, the largest controlled randomised trial of progesterone treatment of threatened miscarriages, were published.[10] A sub-group analysis found that women who had three or more previous miscarriages benefited from progesterone treatment if they presented with bleeding in early pregnancy.

LUTEAL PHASE SUPPORT IN ASSISTED REPRODUCTION

The Practice Committee of the American Society for Reproductive Medicine (ASRM) in 2015 reaffirms the use of progesterone supplementation for luteal phase support in patients undergoing assisted reproductive technology (ART) procedures. This should be distinguished from the treatment of luteal phase deficiency in natural, unstimulated pregnancies, where there is no evidence of benefit in improving pregnancy outcomes.[26] van der Linden reported that progesterone given during the luteal phase was associated with higher rates of live birth or ongoing pregnancy compared with placebo or no treatment. However, the quality of evidence provided by the five RCTs conducted in the late 1980s through 1990s was considered very low quality. Furthermore, when the analysis was restricted to livebirths, there were no differences between both groups.[27] A meta-analysis of eight RCTs comparing oral dydrogesterone and vaginal progesterone found similar efficacy in both drugs for luteal phase support. However, the trials reported surrogates such as on-going pregnancy and miscarriage as the primary outcome, rather than live births.[28]

There is insufficient evidence to recommend a particular type, dose, or route of progesterone administration for luteal phase support and the recommendations in this guideline were based on consensus amongst the expert panel.[27]

PRETERM BIRTH

Preterm birth (PTB) complicates between 7 and 12% of all births yet accounts for more than 85% of all perinatal morbidity and mortality. Its aetiology is multifactorial and pathophysiological mechanisms include intrauterine infection, cervical insufficiency, and increased uterine stretch/distension in the cases of multiple pregnancies.[29] PTB can broadly be classified as spontaneous or medically indicated ("iatrogenic"). A previous PTB is the strongest predictor for a subsequent PTB.[30] However, approximately 20% of preterm deliveries are due to various maternal or fetal indications such as severe preeclampsia or fetal growth restriction. The term medically indicated PTB has been proposed to describe this subgroup. Clearly, progesterone has no role in these women. Cervical shortening is a known risk factor for PTB in both low and high risk populations.[31] The relative risk of PTB was estimated at 6 if <26mm (10th centile), 9 if <22mm (5th centile) and 14 if <13mm (1st centile).[29] The majority of studies on cervical length were performed in midtrimester, coinciding with morphology screening, using thresholds of below 20 mm or 25 mm for intervention and these cut-offs remain the most frequently used in clinical practice.[30] A meta-analysis in 2005 found singleton women with a history of spontaneous PTB, including preterm labour and premature rupture of membranes, who received 250 mg intramuscular 17-α-hydroxy-progesterone caproate (17P) weekly, had lower rates of recurrent PTB (29.3% vs. 40.9%; OR: 0.45; 95%CI: 0.22, 0.93). In addition, subjects allocated to receive 17P had lower rates of birth weight less than 2500g. No differences in rates of hospital admissions for threatened preterm labour or perinatal mortality were noted for subjects receiving progestational agents in general or for those receiving only 17P specifically. Hassan et al.,[32] demonstrated that in a cohort of 458 women, the progesterone group had a lower rate of preterm birth before 33 weeks compared to placebo. Vaginal progesterone was also associated with a significant reduction in the rate of preterm birth before 28 and 35 weeks, respiratory distress syndrome and birth weight <1500g.[33]

A subsequent literature review of all randomised trials between 2003 and 2017 reaffirmed that only two routes of progesterone administration were effective, weekly intramuscular injections of 17P and daily administration of vaginal progesterone suppository of 100-200mg in preventing further PTB, in singleton pregnancies with previous PTB.[34] The purported efficacy of IM 17P and the American College of Obstetricians and Gynecologists (ACOG) recommendation is largely based on data from Meis et al., although the recent trial, 17P to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG) has brought us back to the drawing board.[1,35] This trial which recruited four times more women, including women outside of the USA, showed that 17P did not reduce the risk of preterm labour. Of note, the racial and social demographics in the PROLONG study appear to reflect women of a lower risk group.

For a brief period, questions were raised on the efficacy of progesterone after the publication of the Vaginal Progesterone Prophylaxis for Preterm Birth (OPPTIMUM) trial in 2016. The results of that trial showed that vaginal progesterone did not significantly reduce the risk of PTB or perinatal morbidity and mortality in the entire population or in the subgroup of women with a cervical length ≤25mm. Needless to say, this created significant confusion amongst clinicians. A closer look at OPPTIMUM however, revealed that this study had a very broad inclusion criteria, where more than a quarter of women did not even have a short cervix. Furthermore, there were methodological concerns about the interval between diagnosis, randomisation, and starting progesterone in high-risk women. The National Institute for Health and Care Excellence (NICE) in the UK suggests a cut-off of 25mm be used for intervention, with vaginal progesterone again being the first line for women with no prior PTB but a short cervix of <25mm. However, in women with prior PTB, it recommends either vaginal progesterone or cervical cerclage. Cervical cerclage was recommended as a first line in women deemed to be at the highest risk; those with a short cervix of <25mm and either a history of preterm prelabour rupture of membranes (PPROM) or cervical surgery.[36] In addition, OPPTIMUM did in fact find a reduction in neonatal brain injury and neonatal death but these were not given sufficient emphasis compared to the composite primary outcome, which was non-significant.[37] Romero et al., then performed a meta-analysis using individual patient data, including five high-quality trials and OPPTIMUM to resolve this controversy. A total of 974 women (498 allocated to vaginal progesterone, 476 allocated to placebo) with a cervical length ≤25mm were included and it was found that vaginal progesterone was associated with a significant reduction in the risk of PTB <33 weeks of gestation. Moreover, vaginal progesterone significantly decreased the risk of

respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight <1500 and <2500g and admission to the neonatal intensive care unit.[38] Conde-Agudelo et al., showed that vaginal progesterone was as effective as performing a cervical cerclage in women who could be considered at the highest risk of preterm birth.[39] The authors made an indirect comparison meta-analysis in a cohort of women with singleton pregnancy, previous spontaneous PTB, and a short cervix. Five trials that compared vaginal progesterone versus placebo (265 women) and another five that compared cerclage versus no cerclage (504 women) were included. Vaginal progesterone, compared to placebo, significantly reduced the risk of PTB <35 and <32 weeks of gestation, composite perinatal morbidity/mortality, neonatal sepsis, composite neonatal morbidity, and admission to the neonatal intensive care unit. Cerclage, compared to no cerclage, significantly decreased the risk of PTB <37, <32, and <28 weeks of gestation, composite perinatal morbidity/mortality, and birthweight <1500g. Vaginal progesterone and cerclage were found to be comparable in terms of the reduction of PTB and adverse perinatal outcomes.

Evidence from an updated individual patient meta-analysis by Romero et al. showed that progesterone supplementation prolonged gestation and improved perinatal outcomes in women with twin pregnancies and a short cervix.[5] This contradicted earlier clinical trials which did not take into consideration the cervical length when starting progesterone.[6,7] Further studies are required in this area as the outcome of the meta-analysis was significantly influenced by a single study. A trial involving 134 healthy women with triplet pregnancies on the other hand showed that the rate of fetal loss or preterm birth <35 weeks was similar between women assigned to receive 17P and placebo from 16 to 21 weeks through 35 weeks of gestation.40

CONCLUSION

The merits and benefits of progesterone in various scenarios presenting clinically as miscarriage remains in equipoise. The evidence for the use of progesterone is more robust in the prevention of early preterm birth in women with a short cervix.

ACKNOWLEDGEMENT

The full guideline was conceptualised, drafted and written by the OGSM Progesterone in Miscarriage and Preterm Birth Guideline Committee led by Dr Eeson Sinthamoney and consisted of the following members:

Dr Voon Hian Yan (Sarawak General Hospital), Associate Professor Mukhri Hamdan (University Malaya), Dr Vinodhini Bhaskaran (Sri Kota Medical Specialist Centre), Dr Kavitha Nagandla and Associate Professor Sharifah Sulaiha Syed Aznal (both of International Medical University), Associate Professor Suzanna Daud (Universiti Teknologi MARA UiTM) , Dr Shamala Devi Karalasingam (Institute for Clinical Research), Dr Sundar Gugan Santhana Dass and Dr Chai Bin Shen (both of Sungai Buloh Hospital) and Dr Pravin Peraba (Pantai Hospital Ayer Keroh).

The authors would also like to thank the Director-General, Ministry of Health Malaysia for permission for publication. The time taken by the local and international peer reviewers to siphon the contents of the guideline are much appreciated. The administrative staff of the Obstetrical and Gynaecological Society of Malaysia, Premalatha Subramaniam, Chong Kien Loon, and Jenny Kaur have been invaluable in coordinating the meetings and correspondence.

ETHICAL CONSIDERATION

The guideline from which this CME was derived was initiated by the Obstetrical & Gynaecological Society of Malaysia with an educational grant from Abbott Pharmaceuticals.

CONFLICT OF INTEREST

None of the guideline committee members were paid honorarium. No pharmaceutical representatives were involved in the discussions, or in providing assistance in any form, in the preparation of this guideline. Neither was their opinion sought.

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ASSESSMENT OF LEARNING
Multiple Choice Questions (MCQ)
Each of the following stem has either a TRUE or FALSE answer.

1. A 28-year-old primigravida at 10 weeks of gestation presents to your general practice with complaints of per vaginal spotting. She has otherwise no abdominal pain and your bedside ultrasound scan showed a singleton live fetus, measuring around 9 weeks of gestation. You do not see any other abnormalities and a speculum examination showed a normal vagina and cervix. She is very worried and requests for medications to stop the bleeding. The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Complete bed rest for the next 3 to 7 days
   D. Reassure

2. A 38-year-old lady at 10 weeks of gestation presents to your general practice as her obstetrician is away. This is her fourth pregnancy and she has had three previous spontaneous first trimester miscarriages. Her obstetrician could not identify the cause of her previous miscarriages but previously advised her to see a doctor as soon as she suspected she was pregnant. She is asymptomatic and your bedside ultrasound scan showed a singleton live fetus, measuring around 9 weeks of gestation. She is understandably worried and requests for medications to help "strengthen her pregnancy". The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Folic acid and supplements containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)
   D. Reassure

3. A 38-year-old lady who is 14 weeks pregnant presents to your general practice as her obstetrician is away. This is an IVF pregnancy and she has had a previous spontaneous first trimester miscarriage. She was given progesterone until a few weeks ago but has read about the importance of luteal phase support in early pregnancy. She is asymptomatic but understandably worried and requests for medications to help "strengthen her pregnancy". The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. 8% intravaginal progesterone gel
   D. Reassure

4. A 28-year-old primigravida who is 20 weeks pregnant with a singleton pregnancy has just had a midtrimester anomaly screening and told that her baby was normal. However, the cervical length measured 21mm. She was otherwise asymptomatic. The appropriate management
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Repeat cervical length measurement in 1 week
   D. Reassure

5. A 28-year-old primigravida who is 20 weeks pregnant with a dichornionic diamniotic twin pregnancy has just had a midtrimester anomaly screening and told that her babies were normal. However, the cervical length measured 21mm. She was otherwise asymptomatic. The appropriate management
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone 200mg ON
   C. Vaginal micronised progesterone 400mg ON
   D. Repeat cervical length measurement in 1 week

The many reasons of poor performance/more pertinent reasons for poor student performance

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Dear editor,

In the March 2022 issue of MJM, Puthiaparampil et al (2022) published a paper titled: 'Dropping the non-core subjects from undergraduate final professional examination: How it would impact the results'. In that paper, the authors presented the results of a retrospective analysis of Multiple True False (MTF) and Best Answer Questions (BAQ) of Final Professional Examinations (FPE) of past 4 years. The article showed that the student's performance in 'non-core subjects' was significantly lower compared to that in 'core subjects'. It concluded with the suggestion that 'including the non-core subjects in the FPE overburdens the students, impedes adequate revision of the subjects, and lowers their scores in the final professional examination' and that 'dropping the non-core subjects from MTF and BAQ would improve the students' final scores and would help more students to attain distinction status.'

While the paper highlighted one pertinent issue, upon deeper consideration, we realized that there could be other reasons also why students would perform poorly in examinations. These reasons could be the difficulty level of the questions as well as the validity of the questions (i.e. whether the student is being tested on what he or she is supposed to be tested based on the prescribed curriculum for undergraduate level). Another pertinent issue that should be explored is the inadvertent inclusion of non-core topics in the assessments.

The key to minimize the risk of inclusion of non-core topics is to have a vigorous examination blueprint and to diligently stick to the plan. One of the practical blueprinting techniques is the two-dimensional technique by Coderre et al.[1] recommended two criteria for evaluating the importance of a topic: (1) the impact of the condition and (2) the frequency of the condition. A condition such as cardiac arrest in emergency medicine would be weighted as highly impactful (due to the time-sensitive need for prompt recognition and prompt initiation of chest compression) and highly frequent (as cardiac arrest can occur in any ward, be it in internal medicine, general surgery, obstetric wards, etc.).

In conclusion, as the primary goal of assessment is to ensure that a student has been adequately equipped to function as a safe and competent house officer, the assessment rendered must be a valid one. The key to improving the validity of an assessment is to have a blueprint.

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This article was accepted: 13 June 2022
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Acknowledgement
July Issue 2022

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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