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The Medical Journal of Malaysia

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Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations, or both: emphasise or summarise only important observations in the text.

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

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

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The prevalence of Autism Spectrum Disorder in Down Syndrome children attending the Child Development Centre in Universiti Kebangsaan Malaysia Medical Centre

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ABSTRACT

Introduction: The main objective of this study was to determine the prevalence of Autism Spectrum Disorder (ASD) in Down Syndrome (DS) children attending the DS clinic at Child Development Centre Universiti Kebangsaan Malaysia Medical Centre (CDC-UKMMC) and to assess the appropriateness of using an M-CHAT as an ASD screener in this population. We traced the karyotype results of our study population from their medical record and compared this to study participant with a dual diagnosis of Down Syndrome-Autism Spectrum Disorder (DS-ASD). Lastly, we assessed the awareness among parents attending our DS follow up clinic regarding the possibility of an ASD diagnosis in DS children.

Materials and Methods: This a single-centre cross-sectional study among DS children aged 18-60 months who attend the DS follow up clinic in UKMMC. Overall, 24 children were recruited to our study. The accompanying parent was given the Modified Checklist for Autism in Toddlers (M-CHAT) questionnaire and a data collection sheet prior to their consultation. The chromosomal study was traced from their medical case notes. Children that were eligible for the study had their development assessed using the tool Schedule of Growing Skills II. The diagnosis of ASD was determined by the attending paediatrician using The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria.

Results: The prevalence of dual diagnoses DS-ASD in our study population was 4.2%. Using M-CHAT as a screener, 8 children failed the M-CHAT, of whom only one was diagnosed with ASD. None of the children that passed the M-CHAT was diagnosed with ASD. Only 17 chromosomal study results were available for analysis, 2 children had mosaic DS whereas the remaining was caused by non-disjunction; the only DS-ASD patient had non-disjunction. Regarding parental awareness of dual diagnoses of ASD and DS, about 60% of the parents attending UKMMC clinic were aware of the possibility of ASD-DS diagnosis.

Conclusions: Our results suggest that ASD prevalence in our DS study population is consistent with those previously reported, and that paediatricians managing DS children should be aware of the dual diagnoses of ASD and DS when managing these patients. Even though, we are unable to make a definitive conclusion regarding the use of M-CHAT in this population of children due to the very small sample size, possibly a multi-centre research in the future may help elucidate this issue.

KEYWORDS:
Autism spectrum Autism spectrum disorder, Down syndrome, M-CHAT

INTRODUCTION

Down Syndrome (DS) is the most common recognized chromosomal abnormality and is caused by an extra chromosome 21. DS children have classical features and can be confirmed by karyotype studies. The most common karyotype in DS is non-disjunction and this accounts for about 90% of DS children; Robertsonian translocation and mosaic is less common and has been reported to be between 0.7-4% of cases.[1-3] The incidence of DS increases with increasing maternal age. It has a prevalence of 1:700 live birth worldwide.[4] In Malaysia it is reported that the incidence of Down syndrome is 1:860 to 1:981 live birth.[5]

The latest report by the Center of Disease Control and Prevention has reported that the prevalence of Autism Spectrum Disorder (ASD) in the general population surveyed may be as high as 1.8%.[6] It has also been reported that the diagnosis of ASD in children with concurrent chromosomal or genetic abnormality may also be higher.[7] Literature has reported an ASD prevalence in DS children to be between 2-20%.[8-10]

It is assumed that children with DS are generally affectionate and outgoing.[11] Nevertheless, more recent studies have shown that children with DS can have a dual diagnosis of Down Syndrome-Autism Spectrum Disorder (DS-ASD) which may present with behavioural challenges that are not typically associated with DS children. Children with a dual diagnosis tend to have a distinct behavioural symptomatology as compared to children with the diagnosis of ASD alone. Even though there have behavioural challenges, children with DS-ASD were found to have less severe social impairment as compared to children with the diagnosis of ASD in isolation.[12]

Thus, it is not uncommon for the recognition of dual DS-ASD diagnosis to be delayed as professionals may misinterpret their behaviour to be related to the cognitive and language

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delays.[10] Nevertheless, early diagnosis ASD in DS children could improve the developmental outcome and quality of life for families by the provision of appropriate early intervention.[13] Other than that, families have also reported frustrations and confusion when pervasive behaviours are not consistent with the expectation of a DS child.[13] Thus, timely diagnosis of ASD in these children would be beneficial not only to the child but also to their families and the community that supports them.

With these issues in mind, firstly we wanted to determine the prevalence of ASD in children with DS at the Child Development Centre, University Kebangsaan Malaysia Medical Centre (CDC-UKMMC) as well as the appropriateness of using The Modified Checklist for Autism in Toddlers (M-CHAT) in the DS population. M-CHAT is a recommended ASD screener for children 18-30 months which is available in English and its translation into Malay is publicly available.[14-15] We were also interested to determine if a difference exists between DS children with non-disjunction, Robertsonian translocation or mosaic DS and the diagnosis of ASD. Lastly, we wanted to assess the awareness of the parents attending our clinic regarding the possibility of ASD-DS dual diagnosis in their children, as we believe that a greater awareness would assist these children to obtain an earlier diagnosis and in turn access appropriate support and intervention.

MATERIALS AND METHODS

This was a single-centre cross-sectional study of children with Down Syndrome between 18-60 months old. All children with Down syndrome who agreed to participate in this study seen in CDC-UKMMC from 1 January 2019 until 31 December 2019 were enrolled into the study. Down syndrome children who have moderate to severe hearing or visual impairment after correction with a hearing aid or glasses were excluded in our study. This study received approval from the ethics committee of UKMMC.

There were 68 DS children under follow-up at CDC-UKMMC DS clinic during the study period and 29 children were between 18-60 months old. However, only 24 children were recruited for the study after excluding those that did not agree to participate or did not fulfil the inclusion criteria.

All children and parents who were eligible for the study were given an explanation on their appointment day. One of the parents was requested to complete the M-CHAT form and data collection sheet including questions assessing parental awareness of dual DS-ASD diagnosis. This was followed by a Schedule of Growing Skills II (SGS II) assessment by a trained nurse and an assessment by the attending paediatrician experienced in the diagnosis of ASD. The attending paediatrician would address current medical concerns as well as assess the possibility of a concurrent ASD diagnosis based on the DSM-5 criteria. This includes a comprehensive history taking, physical examination and observation of behaviour during the consultation. Any children with an unclear diagnosis would be discussed and seen in our multidisciplinary clinic. This is a monthly clinic conducted at UKMMC to confirm the diagnosis of children with ambiguous clinical presentation. The professionals involved included a paediatrician, child psychiatrist, child psychologist, occupational therapist, and speech therapist. The karyotype results were traced from the medical records of the patients.

Instruments

a) Schedule of Growing Skills II (SGS II):

SGS II is a developmental screening tool that assesses 10 different domains for children below 60 months of age. It is a tool adapted from the United Kingdom (UK).[16] Its purpose is to provide an accurate and reliable method of developmental screening; it is easy to use and requires little training. It is not an in-depth diagnostic tool; however, it does provide pointers to the nature of the child's problem and assesses a child's development at a point of time. Although it is a British-based tool, SGS-II has been found to be a reliable and accurate tool for assessing development in disabled children in the local context based on a working paper by Haironi and Mariah from University Malaysia Sarawak in 2014.[17] In UKMMC, the SGS II assessments are performed by trained CDC clinic nurses prior to consultation with the paediatric medical team.

The SGS-II has 10 domains and is valid for use in children from birth to 60 months of age. The manual defines 'significant delay' as the developmental age being more than one age band below the chronological age.[16] This assessment uses a focused play based approach which includes clear instructions to guide the administration of the assessment activities as well as guide the gathering of specific information from the parent or caregiver.

For data analysis, we used the SGS-II definition of developmental delay.[16] Any children who were more than the one age band below their chronological age was considered to be delayed.

b) M-CHAT screening

M-CHAT is a screening tool for autism that has been translated to Malay and Chinese to be used in the local healthcare population and recommended for use in toddlers aged 18 months up to 30 months of age.[14] It is a 23-item yes/no parent report checklist that is simple and does require any parent training. It is necessary to train health care workers for accurate interpretation of the results.[14] In Malaysia, it is recommended that children are screened with M-CHAT at 18 and 30 months old.

M-CHAT is a screening tool for toddlers aged between 18-24 months. Early referral for possible diagnosis of ASD was initially recommended for any children who failed either 2 critical items or any 3 items in the M-CHAT questionnaire, based on an early study in 2001 which reported a sensitivity of 0.87 and a specificity of 0.95.[18] In current years, the scoring method has been updated and it is currently recommended that children with a total score of 3 – 6 should have a M-CHAT Follow-Up (M-CHAT/F) administered. A persistent score above the cut of point 3 is able to identify screen positive children, while those with a cut of point of 7 should be referred for evaluation without the need for further M-CHAT/F administration as an additional follow up with a M-CHAT/F will not alter the specificity or sensitivity of the screening test.[19] The positive predictive value in toddlers aged 16-30 months indicates that 54% of children who screen

Table I: Demographic data

	Mean (SD)
Age at SGS II and MCHAT administration (months)	46.2 (10.1)
Father's age (years)	38 (5.5)
Mother's age (years)	37.9 (5.5)
Mother's age at delivery (years)	33.5 (5.1)
	n (%)
Gender	
Male	16 (66.7%)
Female	8 (33.3%)
Race	
Malay	21 (87.5%)
Chinese	3 (12.5%)
Indian / Others	0
Parent's education level	**n (%)**
Father	
Secondary education	11 (45.8)
Post-secondary vocational certificate	1 (4.2)
Tertiary education	11 (45.8)
Not available	1 (4.2)
Mother	
Secondary education	8(33.3)
Post-secondary vocational certificate	1 (4.2)
Tertiary education	15 (62.5)

Table II: M-CHAT results vs. SGS II results

Developmental domain	M-CHAT score 0-2 n (%)	M-CHAT score>3 n (%)
Locomotor		
Delay	13 (54)	7 (29)
No delay	4 (17)	0 (0)
Manipulative		
Delay	11 (46)	6 (25)
No delay	6 (25)	1 (4)
Visual		
Delay	11 (46)	6 (25)
No delay	6 (25)	1 (4)
Hearing & language		
Delay	15 (63)	6 (25)
No delay	2 (8)	1 (4)
Speech & Language		
Delay	17 (71)	7 (29)
No delay	0	0
Social interaction		
Delay	8 (33)	5 (21)
No delay	9 (38)	2 (8)
Selfcare		
Delay	8 (33)	5 (21)
No delay	9 (38)	2 (8)
Cognitive		
Delay	16 (67)	7 (29)
No delay	1 (4)	0 (0)

positive on a 2-staged M-CHAT (M-CHAT and M-CHAT/F) are likely to have ASD and 98% of these toddlers will have clinically significant developmental concern.[20]

M-CHAT has also been used among cognitively impaired pre-school children aged between 16-48 months and M-CHAT has positive predictive value of 60%-80% in this population.[21-22] The same tool has also been used specifically in children with DS, it was found to be a sensitive screening tool, however it's specificity is low for ASD.[9]

ASD diagnosis

The diagnosis of ASD was based on clinical judgement of the attending paediatrician based on The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria.[23] All children who came for follow up were seen by paediatricians experienced with the diagnosis of ASD. Any cases that had an unclear diagnosis were discussed with other members of the child development team.

Clinical diagnosis of ASD based on DSM-IV, DSM-5 and clinical judgment by an experienced clinician in children as young as 16 months is stable over time in 84% of cases. In

our study, all cases were diagnosed by experienced paediatricians and any unclear diagnosis discussed between the professionals and consensus reached. Diagnostic stability is highest when clinical judgment is combined with multidisciplinary team assessment.[24]

Data analysis

The results were analysed using the Statistical Package for Social Science (SPSS) version 20. Descriptive statistics was used. For continuous or linear data, we presented the results in mean and standard deviation, and for categorical data we presented the results in percentages.

RESULTS

The demographic data is presented in table I. The participants in our study were between 18 to 60 months old and approximately two thirds were between 37 to 60 months old. The majority of our study population were boys (66.7%). Overall, 67% of mothers in our study had tertiary education, compared to 45.8% of fathers, and the mean parental age for both were similar.

Out of 24 subjects in our study, only one patient with DS was diagnosed with ASD using DSM-5 criteria.

In our sample, 15 of our children had karyotype study results consistent with non-disjunction DS, whereas 2 had mosaic DS. There were no study participants who had Robertsonian translocation. Results of 7 participants were unavailable.
We found that most children with DS have delay in their language and cognitive development which is not congruent with their social interactive developmental attainment. There was no difference in the developmental profile of DS children with non-disjunction as compared to those with the mosaic karyotype.

Using M-CHAT as a screening tool, 7 children failed the M-CHAT with a total score of 3 or more, and only one of them fulfilled the criteria for ASD diagnosis. None of the children who passed the M-CHAT were diagnosed with ASD, 5 of the children had an M-CHAT score of 0, while another 12 of them had a total score between 1-2.

When the M-CHAT scores were compared against the SGS II score, there was no statistical correlation between the two. However, it was noticed that approximately half of the children who were delayed passed the M-CHAT with a total score of 2 or less. This result is shown in table II.

In general, we found that the children who failed the M-CHAT had relatively lower cognitive scores compared to the other study subjects. Out of the 7 children who failed the M-CHAT, 6 had cognitive scores equivalent to a child younger than 18 months at the point of M-CHAT administration.

The one child with DS from our study who was diagnosed with ASD had severe developmental delay across all domains. He was 37 months; however, his cognitive age was equivalent to a child of 8 months old on the SGS II assessment.

15 out of 24 (62.5%) parents were aware of the presence of dual diagnosis in children. Seven of them received information from their local parent support group, 3 of them from their own reading either via the internet, books, or magazine and only 3 of them received information during follow up from their health care provider and 2 respondents did not answer the question regarding the source of information.

DISCUSSION

In our sample of children only 1 out of 24 was confirmed to have ASD. This small sample size limited our ability to calculate the true prevalence of DS-ASD diagnosis in our study. Review of literature has reported a higher prevalence of ASD in the DS population. The prevalence of ASD in DS children are reported to be between 2-20%.[8-10] The variation in prevalence is partly attributed to use of different study populations, various methodologies and different diagnostic tools.

The developmental screening done in our sample showed that these children had comparatively better social and interactive skills as compared to their language and cognitive developmental domain. This is consistent with literature whereby DS children are generally known to be more sociable and tend to have joint attention that is comparative to typically developing children with the same developmental level, even though the majority of these children have severe delay in language development.[25-29] In addition to language delay, mild to moderate intellectual disability is also prevalent in DS children.[30] Most publications report that children with a dual DS-ASD diagnosis tend to have the lowest cognitive score.[25,31] However, children at all intellectual levels are also at risk of ASD.[32-33] The only child in our study who had a confirmatory diagnosis of ASD was the child with the lowest cognitive score.

M-CHAT has been used in both level 1 screening in a primary care setting as well as a level 2 screening for children with underlying developmental delay or other chromosomal abnormality.[9,34,35] It is a sensitive tool for detecting autism, but specificity is low in children with underlying developmental delay.[9,22] This seems consistent with our sample, whereby, approximately 70% of our children passed the M-CHAT screening despite their developmental delay and only 1 out of the 7 children who failed the M-CHAT screening was diagnosed with ASD. More recent publications have suggested the use of a follow-up telephone interview to reduce the false positive rate of M-CHAT.[18,20,34]

Two out of 17 (11%) children in our sample had mosaic DS. In a Malaysian study on karyotype characteristics of DS children, the percentage of mosaicism was reported as 4.7%.[2] Our findings were higher than expected, however, due to the small sample size, it may not reflect true population prevalence. It is believed that the higher number of abnormal cells will result in a greater manifestation of DS traits and a majority but not all of the studies report a higher IQ in children with mosaic DS as compared to their non-mosaic counterpart.[3,36] We postulated that children with mosaic DS may be less likely to have ASD symptoms and better

developmental outcomes. In our sample we did not find any difference in the cognitive and developmental profiles of children with mosaic DS as compared to their non-mosaic counterpart, and none of the mosaic DS children was diagnosed with ASD. This result is not surprising as ASD is a complex collection of symptoms with varying aetiology and the genetic abnormalities may not be able to be detected at a basic karyotype level.

When parental awareness of dual DS-ASD diagnosis was assessed, more than half of the parents in our study were aware of this possibility. Surprisingly only 3 parents in our sample reported receiving information from a health care professional, and instead most of them received information from their local support group. Even though the numbers were too small to be of statistical significance, this is an important reminder for health care professionals managing children with DS to be aware of the possibility of a dual diagnosis. The same message is also echoed in other previously published reports.[37-38] Previous studies have also supported the importance of parental support groups for the empowerment of parents and to promote better outcomes in children with DS.[39]

In our study, there are a few limitations. Our study was a single centre study, and the sample size was small thus this may not reflect the general population. The diagnosis of ASD was based on clinical judgement and DSM 5 criteria alone without the use of diagnostic tools due to resource and time limitations. Future studies should consider the use of standardized tools for diagnosis of ASD in the study design. In addition, we used SGS II, a developmental screener for assessment of our participant's developmental level. We recognize that a developmental screener can only give a brief snap-shot of child's developmental level and is not equivalent to other diagnostic developmental assessment tools, which can give a more thorough and in-depth assessment of a child. However, this tool was chosen in our study due to the resources available to us at that time. However, we found that using SGS II as a tool had benefits, including ease of administration, accessibility and convenience in our local setting as well as a simple result display that is beneficial to aid families to understand developmental concerns of their child and areas that require more attention. This may be a reasonable alternative in resource-limited settings. Despite these limitations, we believe this preliminary data could create greater awareness amongst clinicians managing DS children and encourage future studies to be done in collaboration with other institutions.

CONCLUSIONS

We would like to highlight that ASD is not uncommon in the DS population and thus it is important to improve the awareness amongst clinicians and professionals who are serving them. Even though, we are unable to make a definitive conclusion regarding the use of M-CHAT in this population of children due to the very small sample size, possibly a multi-centre research in the future may help clarify this issue Lastly, professionals managing children with DS should routinely discuss possibilities of comorbidities and dual diagnosis such as ASD with parents and empower them to seek support from relevant health professionals as well as local parent support groups.

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Analysis of paediatric cochlear implant candidacy: Single centre, retrospective observational study

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ABSTRACT

Introduction: The criteria for cochlear implantation can differ among countries or even among regions in the same country. Patient selection is important for the identification of those children who can benefit the most from cochlear implants. A number of patients who are possible cochlear implant candidates do not meet the assessment criteria; and some of these requirements are modifiable components.

Materials and Methods: This single-centre, cross-sectional study used secondary data from 2014 until 2018. A consecutive sampling method was applied and a final sample size of 73 samples was achieved. Potential prelingual hearing loss candidates for cochlear implant aged less than 48 months old in Raja Permaisuri Bainun Hospital (HRPB), Ipoh Perak were included in this study. The candidacy selection outcome was analysed and reported as proportions. The associations between the evaluation criteria and outcome were examined using regression analysis.

Results: Of the 73 potential candidates, only 17 (23%) were selected to receive cochlear implants. Bivariate analysis identified hearing compliance, behaviour, medical contraindications and family commitment as significantly associated with cochlear implant evaluation outcome. However, multivariate logistic regression revealed only family commitment as a significant predictor of the outcome of the implant candidacy evaluation (OR 44.7; 95%CI 3.11–643.4; p<0.005).

Conclusion: Family commitment, a modifiable element, was the key factor affecting the selection of candidates. Addressing the reasons for this effect could increase the number of potential candidates who ultimately receive implants.

KEYWORDS:
cochlear, implant, candidacy selection, paediatric, family commitment

INTRODUCTION

Approximately 466 million people worldwide suffer from hearing loss, and many of these (34 million) are children.[1] Disabling hearing loss in children is defined as a hearing loss greater than 30dB in the better hearing ear. Hearing loss can be attributed to a number of factors, such as hereditary conditions, birth defects, infectious disorders, chronic ear infections, drug abuse, exposure to unnecessary noise and aging. The World Health Organization (WHO) estimates that about 60% of childhood hearing loss could be eliminated by preventive measures. When the circumstances are inevitable, interventions are required to ensure that children reach their full potential.[2]

Children's hearing is crucial for their understanding of spoken language and for academic achievements and social participation;[3,4] therefore, hearing loss is a serious obstacle to both education and social integration. Prelingual hearing loss has a detrimental impact on all aspects of language learning, but the influence is most profound on phonology, morphology, advanced vocabulary and syntax.[5] For this reason, children with hearing loss can benefit immensely from detection early in life, before the age of 6 months, and from receiving targeted interventions.[6,7] The recommended intervention plans include family counselling, hearing aid fittings, audio training, language learning and educational programs based on the needs and abilities of the infant or child.[8]

One study has shown that hearing-impaired children who receive appropriate and early hearing aid assessment and fitting at 3 months of age, followed by cochlear implantation at 9 months of age, will achieve normal language development in up to 96% of the cases.[9] Previous research in Malaysia determined that paediatric cochlear implantees under the age of 4 years showed better long-term results in terms of ability to communicate orally and to attend mainstream education compare to older age at implantation.[10] Children with severe and profound hearing loss benefit the most from cochlear implants in terms of speech comprehension and language development.[11]

Since December 2012, a total of 324,200 cochlear implants have been implanted worldwide. Approximately 58,000 adults and 38,000 children were implanted in the United States of America.[12] Between 2008 and 2018, a total of 380 cochlear implants were performed in Malaysia in 283 prelingual deaf children.[13] The interdisciplinary approach recommended by the NICE Guideline is the current standard of care for the selection of implant candidates.[14] A decision on the candidacy is reached by subjecting the child to medical, audiological and speech–language assessments. In addition,

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successful cochlear implant outcomes also require a number of steps that range from adequate preoperative amplification with hearing aids to uncomplicated surgery.

In Malaysia, cochlear implant candidates are chosen through a comprehensive multidisciplinary evaluation by the Satellite Hospital Committee, with final approval decided by the National Ministry of Health Cochlear Implant Committee at meetings held at regular intervals. The satellite committees are divided into the North, Central, South, East, Sarawak and Sabah zones. Every satellite committee consists of surgeons, audiologists, speech therapists, paediatricians, radiologists, medical social services officers, psychologists, occupational therapists and other related professionals. All potential implant candidates are evaluated by the Satellite Committee, and only those candidates who meet the selection requirements are sent to the National Cochlear Implant Committee for approval. The selection is based on the parameters set out in the Operational Policy of the Otorhinolaryngology Service.[15] Each child must be assessed from a variety of perspectives, including their physical, neurophysiological, physiological, audiological and family aspects.

One study found that about 70% of countries have national or local guidelines in place that regulate the candidacy for implantation. Another 20% have guidelines, but whether a patient is a candidate for implantation is decided by the individual clinical team. The remaining 10% of countries have no guidelines in place.[16]

In Malaysia, candidates for cochlear implants are chosen based on certain selection criteria. However, a number of patients who are potential cochlear implant candidates do not meet these criteria. The aim of this study was therefore to explore these candidate selection criteria and the factors that can affect the selection outcome. Recognising the attributes of failed candidacy selection may enable the establishment of effective strategies targeted at these factors, thereby increasing the number of suitable candidates.

MATERIALS AND METHODS

Study design

This was a single-centre, cross-sectional analysis using secondary data from 1 January 2014 to 31 December 2018. The data were taken from the minutes of the Satellite Committee meeting and from the Otorhinolaryngology (ENT) clinical records. Data on the decision of the candidacy selection and assessment of each selection criterion for cochlear implants were captured. Data capture was achieved using a structured checklist (see Appendix 1).

Study population and study sample

The study included candidates with prelingual hearing loss who were less than 48 months of age. The study population consisted of candidates for cochlear implant evaluation at Raja Permaisuri Bainun Hospital (HRPB). HRPB is one of the cochlear implant referral centres in the Northern Region of Malaysia. Candidates who were eligible for a second implant and with a pending selection decision by the Cochlear Implant Satellite Hospital Committee were excluded. Any candidates who had been transferred to another hospital for continued treatment were also excluded, as this would have had an effect on the findings. A consecutive method of sampling was used. In total, 73 candidates were eligible and were included.

Evaluation criteria for cochlear implants in HRPB (adopted from the Cochlear Implant Service Operational Policy Malaysia 2017)[15]

Candidacy evaluation is critical for determining the suitability of the patient for cochlear implantation. The eligibility evaluation for paediatric cochlear implantation was based on the following components:

a) Age of the candidate

In Malaysia, the prelingual child should be implanted before the age of 48 months, according to the cochlear implant guideline. Govaerts and colleagues (2002) showed that implantation before the age of 4 years seemed crucial to prevent permanent loss of auditory output.[17] Applicants in this age group therefore fulfilled the age criterion.

b) Audiology

The audiology assessment is used to define the current aural condition and to set a benchmark for aural rehabilitation after cochlear implantation. It consists of a pure tone audiometry assessment, a hearing aid compliance assessment and a sound-field threshold. Generally, the pure tone audiometry was conducted to ensure that candidates had a hearing loss at a level of 70 dB or higher. According to current US Food and Drug Administration guidelines, the indication for cochlear implantation is a bilateral profound sensorineural hearing loss (> 90dB) in children aged 9–24 months and a severe (70-85dB) to profound hearing loss in those aged 2–17 years.[18] A paediatric candidate also had to undergo a hearing aid testing period of at least 3 months prior to cochlear implantation.[19] The candidate needed to comply with wearing the hearing aid for at least 8 hours a day. Compliance with the wearing of a hearing aid was determined by a review of the data logging that was integrated into the hearing aid to track the average hours of use every day.

c) Speech and Language

Speech and language assessment is used to evaluate any progress in speech and language skills with the continued use of hearing aids during the trial period. Candidates receive stimulus response training (home-based program) consisting of a series of hearing (listening) exercises and lessons, receptive language (comprehension), expressive language (what the child says), speech (how the child speaks), pragmatics (social communication) and comprehension (perception). Appropriate behaviour towards stimulus–response training should be demonstrated. The behaviour of the candidates would then be classified as appropriate or inappropriate by the speech therapist. The training was customised to suit the individual needs of the candidate. Parental interaction with the home-based program was also assessed in various ways, such as by completion of homework and enhancement of the child's speech performance and learning behaviour.

Table I: Demographics of candidates for the Cochlear Implant Candidacy Evaluation

Characteristic	Frequency (%) (n=73)
Age (month), Mean (SD)	25.4±10.76
0-12 months	13 (17.8)
13-24 months	21 (28.8)
25-36 months	24 (32.9)
37-48 months	15 (20.5)
Gender	
Male	46 (63.0)
Female	27 (37.0)
Candidacy selection	
Selected	17 (23.3)
Rejected	56 (76.7)

Table II: Aided response by using hearing aids at low and high frequency

Aided response	High Frequency		Low Frequency	
	n	(%)	n	(%)
No response	14	(18.9)	16	(21.9)
Response out of speech range	44	(60.3)	32	(43.8)
Response in speech range	7	(9.6)	17	(23.3)
Defaulted	8	(11.0)	8	(11.0)

Table III: Medical and anatomical contraindications for cochlear implant surgery

Contraindications	Frequency (%) Total= 73
Medical	
Absolute	18 (24.7)
Relative	1 (1.4)
Mixed (Absolute & Relative)	4 (5.5)
No	50 (68.5)
Anatomical	
Absolute	5 (6.8)
Relative	9 (12.3)
Defaulted	13 (17.8)
No	46 (63.0)

Table IV: Absolute and Relative Medical contraindications for cochlear implant surgery

Medical Contraindications*	Frequency (%)
Absolute	
Global Developmental delay	
- Brain/Spine malformation	14 (63.6)
- Genetic	6 (27.3)
- Brain infection	2 (9.1)
Relative	
Medical conditions	1 (20)
Epilepsy	4 (80)
Anatomical contraindication*	
Absolute	
Cochlear nerve aplasia	2 (40)
Cochlear aplasia	3 (60)
Relative	
Cochlear nerve hypoplasia	5 (50)
Cochlear hypoplasia	5 (50)

*Subjects are possible to have more than one contraindication.

Table V: Factors associated with the Cochlear Implant candidacy selection outcome (using bivariate and multivariate analysis regression analysis)

Variable	Crude OR (95% CI)	p-value*	Adjusted OR (95% CI)	p-value
Gender				
Male	**Reference**		**Reference**	
Female	0.44 (0.13-1.53)	0.2	0.25 (0.01-3.41)	0.3
Hearing compliance				
No	**Reference**		**Reference**	
Yes	26.8 (6.4-115.03)	<0.01	8.8 (0.44-174.4)	0.15
Behaviour				
Inappropriate	**Reference**		**Reference**	
Appropriate	31.16 (3.84-253.08)	0.001	6.32 (0.42-94.43)	0.18
Medical contraindications				
No	**Reference**		**Reference**	
Yes	0.09 (0.01-0.78)	0.028	0.27 (0.01-5.44)	0.39
Anatomical contraindications				
No	**Reference**		**Reference**	
Yes	0.14(0.02-1.2)	0.07	0.07 (0.001-3.32)	0.17
Family commitment				
No	**Reference**		**Reference**	
Yes	112 (12.79-980.89)	<0.01	44.73 (3.11 – 643.4)	0.005

*p value <0.25 was taken to include the variables in the multivariate logistic regression analysis.

d) Medical considerations

Medical assessment is carried out with the aims of facilitating the selection of patients, of establishing realistic expectations and of developing an effective recovery plan. Absolute contraindications can include severe global developmental delay, extreme mental retardation to co-operate with speech training, acute or chronic otitis media and mastoiditis without disease eradication. Other medical problems, such as respiratory, cardiac and haematological problems or untreated epilepsy, served as relative contraindications.[20]

e) Anatomical considerations

Preoperative assessment of the cochleovestibular anatomy was performed in all candidates. The goal was to determine the presence of cochleovestibular defects that inhibit implantation. Absolute contraindications for the implant were cochlear nervous aplasia and/or cochlear aplasia, whereas the relative contraindications were cochlear nervous hypoplasia and/or cochlear hypoplasia.[21]

f) Family

The family was briefed by the clinical team regarding the results of the cochlear implant assessment and was given a thorough description of the cochlear implant procedure. The adherence to clinical appointments was also assessed by the clinical team. Families or candidates should be well motivated and willing to engage in the medical appointments that are required for the optimum use of the device.

Statistical analysis

The prevalence of candidates selected to receive a cochlear implant and the descriptive analysis of the independent variables were reported as proportions. We performed univariate and multivariate logistic regression analyses using SPSS 20.0 software. Odds ratios (OR) were reported with their respective 95% confidence intervals (CI), and values of $P < 0.05$ were considered statistically significant.

RESULTS

Demographic characteristics of candidates for cochlear implant candidacy evaluation

A total of 87 candidates were assessed by the HRPB Cochlear Implant Satellite Hospital Committee during the study period. Only 73 candidates were deemed eligible for the study. Among these, 17 (23.3%) candidates were ultimately selected to receive a cochlear implant. The mean age of the candidates was 25 months (SD±10.76), and most of them were males (67%) and their demographic characteristics are shown in Table I.

Severity of hearing loss

All candidates had profound or severe hearing loss in either the right or the left ear. 68.5% of the participants had a profound hearing loss in the right ear and 74.0% in the left ear. Similarly, 27.4% of the candidates had severe hearing loss in the right ear and 20.5% in the left ear. Overall, 3 candidates demonstrated an improvement in their hearing and were removed from the selection process.

Hearing aid use and the aided response using hearing aids at low and high frequency

Overall, 67.1% of the subjects were not compliant in wearing their hearing aid, 30.1% were compliant and 2.7% of the subjects defaulted in their follow-up appointment at the audiometry clinic. Table II shows that the aided response at high or low frequency mainly fell outside the speech range. The aided response of the candidates either fell outside the speech range or no response was seen at high or low frequency.

Speech and language

More than half (52.1%) of the subjects showed inappropriate behaviour towards stimulus response training by a speech therapist. In fact, the majority (67.1%) of the family members of the candidate did not commit to the home-based programme.

Medical and anatomical contraindications for cochlear implant surgery

Of the 73 candidates, 23 (31.5%) were found to have medical contraindications (Table III). Among them, 24.7% of the candidates had absolute medical contraindications in the form of severe global developmental delay (GDD). The causes of GDD were congenital brain or spinal malformation (63.6%), followed by genetic causes (27.3%) and brain infection (9.1%) (Table IV). A further 14 (19.2%) candidates had anatomical contraindications for cochlear implant surgery. As indicated in table IV, more than half the candidates had relative anatomical contraindications.

Candidates that fit all criteria except family factors

Among all the evaluation criteria, the family factor is the only one that is potentially modifiable. Unfortunately, 4 (7.1%) candidates were not selected for cochlear implantation solely due to failing to meet this criterion.

Determinants of cochlear implant selection outcome

Table V shows the bivariate and multivariate analysis of factors associated with the cochlear implant selection outcome. The bivariate analysis showed that hearing aid compliance, behaviour, medical contraindications and family commitment were significantly associated with cochlear implant evaluation outcome; however, the subsequent multivariate logistic regression revealed only family commitment as a significant predictor of implant candidacy evaluation outcome.

DISCUSSION

In this study, the 23.3% uptake rate of cochlear implantation by potentially suitable candidates aged less than 48 months old was considerably lower than in other countries. For example, in the United States of America[22], more than 50% of children with profound hearing loss receive at least one cochlear implant.

Published data have revealed that patients who were implanted before the age of 24 months were more likely to acquire age-appropriate spoken language. Nevertheless, in our study, the majority of children (53.4%) were only assessed for cochlear implant candidacy at an age older than 24 months. The candidates who underwent cochlear implantation were also anticipated to be older, and this could have an impact on their post-surgery speech outcomes. The mean age of children undergoing surgery was 40.1 months in Malaysia.[13] Children born with sensorineural hearing loss and implanted before the age of 42 months have shown age-appropriate latency responses within 6 months of cochlear implantation.[23]

Cochlear implants for children in Malaysia have been entirely supported by national funding. The candidacy criteria are therefore comparatively more restrictive than in other countries with purely self-financing models. Malaysia has a national policy in place that regulates the candidacy for implantation, and a multidisciplinary team decides whether an individual is a suitable candidate. The results of this study suggest that the only significant predictor of cochlear implant eligibility was the commitment of the family to the continuous auditory learning and assessment program offered by the otorhinolaryngology team. This was considered to be the most important component among all the criteria, most likely due to the degree of participation of the family in the pre-and post-operative stages that are critical in the process of recovery of the deaf child. A national survey of paediatric cochlear implant audiologists conducted by Kirkham identified parental factors (93%) as significant predictors of cochlear implant rehabilitation outcomes.[24] Holt et al. also found that the family environment affected the cochlear implantation outcomes of language development in prelingually deaf children between 0.7 and 6.8 years of age.[25]

Children with additional disabilities, such as cognitive disabilities, challenge the ability of the clinician to assess the possible value of a cochlear implant. The current literature indicates that the majority of children with multiple disabilities continue to make progress, although often at a slower pace than in children without additional disabilities. Children with additional disabilities and with motivated families should therefore be given the same opportunity to have access to hearing and to develop their communications skills as any other child with hearing difficulties.[26]

The 10-year report of the National Ministry of Health Cochlear Implant Program revealed that the only factor influencing the post-implant functional outcome was household income.[13] The social demographics of the family, such as the parents' level of education and the household income, were not explored in the present study. These factors may influence the family's commitment to clinical appointments.

Strengths

This is the first study to evaluate the association between the selection criteria for cochlear implants and the outcome of candidacy selection in Malaysia. Our study is also the first to assess the uptake rate of cochlear implants by potentially suitable candidates younger than 48 months of age in Malaysia.

Limitations

The sample size in this study was relatively small, as shown by the wide confidence interval in the statistical analysis. This research also only included those cochlear implant candidates who were assessed by the Cochlear Implant Satellite Hospital Committee in Perak, Malaysia. The generalisation of these results is therefore limited to local settings.

Implications for practice

These results demonstrate the need for education awareness programs to improve parents' understanding of the indications, significant benefits and reasonable risks of cochlear implantation for deaf children. In addition, family responsibilities, such as engagement in the planning and implementation of therapeutic interventions, should also be highlighted assiduously in counselling. This will also potentially improve the dedication of the family to the continuous auditory learning and assessment program offered by the clinical team. The reasons for poor family commitment should be explored; these are likely multi-

factorial and could include competing priorities for the child (e.g. the child was scheduled for multiple appointments), travel difficulties, family dynamics and household income. In the future, a qualitative study that takes into account the perspectives of the family may be useful for identifying the challenges and for learning together with the family about different ways of dealing with obstacles and difficulties in the course of cochlear implantation. A number of factors are related to failed cochlear implant candidate selection; however, the primary predictive factor is poor family commitment. This is a factor which can be changed, and future studies should probe the underlying reasons to allow other potential cochlear implant candidates to benefit from this technology.

CONCLUSION

Given the proven benefits of cochlear implantation in children, it is likely that not all children who are potential candidates will receive cochlear implants. The main predictive factor associated with the outcome of the candidacy selection was the degree of family participation in the assessment and speech and language training programme. A number of factors are related to the rejection of a candidate for a cochlear implant, but poor family commitment is the key predictive factor. This is a factor that can be changed, and future studies should look at the reasons for poor family commitment that prevents cochlear implant candidates from benefiting from this technology.

CONFLICT OF INTEREST

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ETHICS

The study has been registered with the National Medical Research Register (NMRR-19-1673-48993) and obtained ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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ORIGINAL ARTICLE

Outcome of chest re-exploration for haemostasis in intensive care unit post-cardiac surgery: A retrospective analysis

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ABSTRACT

Introduction: Chest re-exploration is potentially life-saving in the treatment of early post-operative complications of open-heart surgery such as for surgical haemostasis, hemodynamic instability, and cardiac arrest. The procedure is often performed in the intensive care unit (ICU) rather than in the operating theatre (OT). The incidence of chest re-exploration may range from 2 to 12%. To analyse the complications of patients who underwent chest re-exploration in the ICU for haemostasis after heart surgery vs in those who were operated in an OT. Secondary outcome measured is all-cause mortality in the patients involved.

Materials and Methods: This is a retrospective analysis of patients' medical records who underwent chest re-exploration in the ICU for haemostasis over a 2-year period (2019 to 2020). The cases which needed re-exploration for haemostasis were divided into two groups: cases conducted in those ICU and those conducted in the OT. Complications post-chest re-exploration were measured and categorized into renal failure needing dialysis, pulmonary complication, gastrointestinal complication, heart failure, pericardial effusion, fever, and surgical site infection.

Results: 4406 cases of open-heart surgeries were analysed. 351 of the patients underwent chest re-exploration, and majority of the cases were re-explored for haemostasis (88.9%). 64.2% of the chest re-exploration were conducted in the ICU. 21.9% patients who underwent post-chest re-exploration in the ICU died, while 13.1% of the patients died post- chest re-exploration in the OT. From the total number of cases of chest re-exploration, 75.9% of patients who had chest re-exploration in the ICU developed complication, whereas patients who developed complication post-chest re-exploration in the OT were 35.1% (p-value < 0.001).

Conclusion: Chest re-exploration in the ICU for post-cardiac-surgery patients showed a higher percentage of complications, which contributes to mortality.

KEYWORDS:
Chest Re-exploration, Haemostasis, Post-cardiac Surgery, Intensive Care Unit, Operation Theatre

INTRODUCTION

Chest re-exploration is potentially life-saving in the treatment of early post-operative complications of open-heart surgery, for example, surgical haemostasis, hemodynamic instability, and cardiac arrest.[1] The overall incidence of re-exploration for bleeding ranges from 2.3 to 6%.[2-6] Bleeding post-cardiac surgery increases the rate of re-exploration, length of hospital stay, requirement of blood transfusion, and its cost.[7] The procedure is often performed in the intensive care unit (ICU) rather than the operating theatre (OT), which allows a more immediate re-exploration to be conducted. However, comparative to the OT, an ICU does not provide an environment which is as sterile, conferring greater mortality and morbidity.

The data in the literature on chest re-exploration for resuscitation is limited, as compared to the number of chest re-exploration for haemostasis. Therefore, the aim of this study is to analyse the outcome of patients who underwent chest re-exploration in the ICU vs those who underwent the procedure in an OT for haemostasis after heart surgery, and to look at the patients' all-cause mortality, post re-exploration.

MATERIALS AND METHODS

This is a retrospective analysis of patients' medical records who underwent chest re-exploration in the ICU for haemostasis over a 2-year period (2019 to 2020) in the Department of Cardiothoracic Surgery, National Heart Institute. The study included first-time chest re-exploration for routine cases of coronary surgeries, valve procedures, and aortic surgeries. The cases which needed re-exploration for haemostasis were divided into 2 groups: cases conducted in the ICU and in the OT. The demographic data of patients, indication for re-exploration, timing and findings of the re-exploration, and the clinical outcome were analysed and recorded using Mann–Whitney U test. The exclusion criteria for this study involved patients aged <18 years, immunocompromised, and those who underwent ventricular assist device implantation surgeries and/or paediatric surgeries, chest re-exploration for deep sternal wound infection, and those who needed chest re-exploration for cardiac arrest and resuscitation. All decisions for chest re-exploration were made by the cardiothoracic consultant surgeon who performed the primary heart surgery.

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Table I: Demographic and clinical data of the subjects recruited for this study based on the location where chest re-exploration was performed

Variables	ICU, N (%)	OT, N (%)	All, N (%)	p-value
Total No. of Cases	192 (100)	107 (100)	299 (100)	
Gender				
Female	47 (24.5)	17 (15.9)	64 (21.4)	0.083
Male	145 (75.5)	90 (84.1)	235 (78.6)	
Age				
Mean ± SD	60.7 ± 11.5	60.8 ± 10.5	60.72 ± 11.12	0.696
Median (Min, Max)	62.4 (22.3,80.4)	61.7 (21.1,85.4)	62.2 (21.1,85.4)	
BMI				
Mean ± SD	26.1 ± 4.9	26.1 ± 4.1	26.12 ± 4.63	0.752
Median (Min, Max)	25.4 (16.0,43.0)	25.1 (19.0,36.6)	25.4 (16.0,43.0)	
Angina Status				
CSS (NO SIGN)	60 (31.4)	38 (35.5)	98 (32.9)	0.418
CSS1	72 (37.7)	47 (43.9)	119 (39.9)	
CSS2	42 (22.0)	16 (15.0)	58 (19.5)	
CSS3	13 (6.8)	4 (3.7)	17 (5.7)	
CSS4	4 (2.1)	2 (1.9)	6 (2.0)	
NYHA				
NYHA I	70 (36.6%)	46 (43.0%)	116 (38.9%)	0.124
NYHA II	94 (49.2%)	55 (51.4%)	149 (50.0%)	
NYHA III	24 (12.6%)	6 (5.6%)	30 (10.1%)	
NYHA IV	3 (1.6%)	0 (0.0%)	3 (1.0%)	
Diabetes				
No	87 (45.8%)	46 (43.0%)	133 (44.8%)	0.641
Yes	103 (54.2%)	61 (57.0%)	164 (55.2%)	
Hypertension				
No	36 (18.8%)	19 (17.8%)	55 (18.5%)	0.816
Yes	155 (81.2%)	88 (82.2%)	243 (81.5%)	
Hyperchlolesterolemia				
No	46 (24.5%)	18 (17.1%)	64 (21.8%)	0.146
Yes	142 (75.5%)	87 (82.9%)	229 (78.2%)	
Renal Disease				
No	100 (57.5%)	56 (56.6%)	156 (57.1%)	0.884
Yes	74 (42.5%)	43 (43.4%)	117 (42.9%)	
Urgency				
Elective	128 (68.1%)	87 (81.3%)	215 (72.9%)	0.048
Urgent	53 (28.2%)	18 (16.8%)	71 (24.1%)	
Emergency	7 (3.7%)	2 (1.9%)	9 (3.1%)	

Chest re-exploration for all patients in the department was practiced in a routinely manner, except that the patient remains in the ICU bed and attached to all the necessary monitoring equipment, instead of being transferred to the surgical table. Our ICU is divided into cubicles of 2 to 4 beds, with curtains to isolate individual bed spaces. All cubicles are separated from one another via a sliding door. Each re-exploration team was led by a consultant surgeon or a senior registrar, assisted by a medical officer or a surgical assistant, along with OT nursing personnel trained in basic theatre techniques, all of whom were scrubbed.

The procedure was conducted under general anaesthesia, performed by the anaesthetist on-call. The patient was draped via the usual manner using povidone and sterile drapes. Post-incision, soft tissue and sternal edges were inspected for any bleeding points. Clots which are present in the chest cavity were evacuated and all operative sites were inspected systematically for any active bleeding. Any detected bleeding points were secured via stainless-steel clips, sutures, diathermy, or adequate application of thrombostatic material, for example, Surgicel. For cases in which haemostasis was secured, the chest cavity was cleaned and the drainage tubes were cleared for any clotted blood, prior to sternal wiring via stainless steel wires. Post-sternal wiring, the sternum was again inspected for any bleeding. Subcutaneous tissue and skin were closed with absorbable suture material. The cases in which haemostasis was uncontrollable surgically, the open chest was packed with adequate number of swaps. The chest cavity was then covered with a piece of sterile latex. Stat dose of antibiotics such as vancomycin was also commenced post-chest re-exploration.

During re-exploration, traffic is restricted only at the patient's bed space. The criteria used in deciding for chest re-exploration vary, depending on the clinical judgement of the senior registrar on-call in managing these patients. The decision for chest re-exploration will be based on the combination of a number of aspects, namely the patient's general condition as a whole, the amount of chest tube drainage per hour, the patient's input–output balance, urine output, central venous and blood pressure trend, and the haemoglobin level.

RESULTS

Between January 2019 and December 2020, 4406 cases of open-heart surgeries were performed. Around 351 of the patients (7.97%) underwent chest re-exploration, where a majority of the cases were re-explored for haemostasis

Table II: Types of Surgery Involved & Operative Characteristics of Patients Underwent Chest Re-exploration for Haemostasis in 2019–2020

Location	ICU, N (%)	OT, N (%)	All, N (%)	p-value
Total No. of Cases	192 (100)	107 (100)	299 (100)	
Type of Surgery				
CABG	122 (63.5)	79 (73.8)	201 (67.2)	
CABG + Valve	24 (12.5)	11 (10.3)	35 (11.7)	
Valve	31 (16.1)	10 (9.3)	41 (13.7)	
Aortic	8 (4.2)	0 (0)	8 (2.7)	
Others	7 (3.6)	0 (0)	7 (2.3)	
Cardiopulmonary Support				
On Pump	191 (99.5%)	107 (100.0%)	298 (99.7%)	0.455
Off Pump	1 (0.5%)	0 (0.0%)	1 (0.3%)	
Bypass time (Min)				
Mean ± SD	129.3 ± 64.9	113.8 ± 47.8	123.7 ± 59.7	0.128
Median (Min, Max)	110.5 (36.0,332.0)	105.0 (44.0,273.0)	109.0 (36.0, 332.0)	
Cross clamp time (Min)				
Mean ± SD	97.2 ± 51.0	87.3 ± 40.6	93.54 ± 47.65	0.182
Median (Min, Max)	84.0 (23.0,274.0)	78.0 (33.0,237.0)	82.0 (23.0, 274.0)	
Post-op Stay (Day)				
Mean ± SD	18.7 ± 21.3	16.0 ± 20.8	17.76 ± 21.15	0.159
Median (Min, Max)	12.0 (1.0 ,162.0)	9.0 (2.0, 160.0)	11.0 (1.0, 162.0)	
Outcome				
Alive	150 (78.1%)	93 (86.9%)	243 (81.3%)	0.062
Death	42 (21.9%)	14 (13.1%)	56 (18.7%)	
Complication				
Renal failure need dialysis	53 (27.9%)	20 (20.2%)	73 (25.3%)	0.153
Pulmonary complication	37 (19.7%)	14 (14.1%)	51 (17.8%)	0.243
GI Complication	15 (8.2%)	7 (6.7%)	22 (7.6%)	0.663
Heart Failure	13 (6.9%)	5 (4.7%)	18 (6.1%)	0.450
Pericardial Effusion	69 (35.9%)	32 (30.2%)	101 (33.9%)	0.316
Fever	29 (15.3%)	17 (15.9%)	46 (15.5%)	0.886
Surgical Site Infection				
No	176 (94.1%)	94 (90.4%)	270 (92.8%)	0.238
Yes	11 (5.9%)	10 (9.6%)	21 (7.2%)	

(88.9%) in the National Heart Institute. 64.2% of the total number of cases of chest re-exploration were conducted in an ICU. A higher percentage of patients who underwent post-chest re-exploration in the ICU were deceased (21.9%), compared to those in the OT group (13.1%), having a *p*-value of 0.062.

As shown below are also the demographic characteristics for the patients involved. For both ICU and OT groups, all chest re-exploration cases consist of more male than female population, with the mean age of 60 years and a mean BMI of 25. Majority of the re-exploration cases for both groups mainly consist of patients who were diagnosed as having hypertension (81.5%), diabetes mellitus (55.2%), and/or dyslipidemia (78.2%). Most cases involving chest re-exploration for haemostasis were the ones admitted for elective surgery (72.9%; *p*-value, 0.048), followed by urgent cases (24.1% and emergency cases being the least involved, with the *p*-value of 0.048).

Based on Table II, the cases were categorized into 5 types: isolated coronary artery bypass grafting (CABG) surgery, CABG and valve surgery, isolated valve surgery, isolated aortic surgery, and others, for example, excision of thoracic tumour, which does not contribute significantly in this study. Out of 299 cases of chest re-exploration for haemostasis, 67.2% were CABG cases, followed by valve cases (13.6%), combined CABG and valve cases (11.7%), and others. Patient who underwent CABG were listed as the majority group to be re-explored in both an ICU and an OT. The operative characteristics of patients who underwent chest re-exploration for haemostasis in 2019 to 2020 were shown. The least percentage of mortality involved were patients who underwent chest re-exploration in an OT (13.1%). Complications of post-chest re-exploration for haemostasis were divided into 7 categories: renal failure needing dialysis, pulmonary complication, gastrointestinal (GI) complication, heart failure, pericardial effusion, fever, and surgical site infection. Patients in the ICU group showed higher percentage of having complications post-chest re-exploration for haemostasis as compared to those in the OT group. Most of the patients did not experience surgical site infection in both the groups (92.8%).

For the patients who were deceased post-chest re-exploration, the sources of bleeding/tamponade were identified as follows: pericardial effusion, bleeding from the internal mammary arterial bed, sternal bleed, bleeding from the graft, generalized bleeding, and others. Based on Figure 1, both the ICU and the OT groups showed pericardial effusion with most common source of chest re-exploration (ICU, 49%; OT, 29%). There was no mortality caused by bleeding from the internal mammary arterial bed in either group. The types of primary surgery done for those who needed chest re-exploration for haemostasis in an ICU, relating to the patient's status were shown here. The number of deceased patients' post-chest re-

Table III: Logistic regression analysis of factors predicting mortality caused by chest re-exploration

Univariable Predictors of Mortality Dependent variable: Mortality Variable	Univariate Analysis				p-value
	Beta	Odd Ratio (OR)	95% Confidence Interval for Difference		
			Lower Bound	Upper Bound	
Gender; Female = 1 as references	-0.598	0.550	0.286	1.056	0.073
Age (Year)	0.051	1.052	1.018	1.087	0.002
BMI	-0.015	0.985	0.914	1.061	0.688
Angina Status; CSS (NO SIGN) = 1 as references					
CSS1	-0.091	0.913	0.439	1.902	0.809
CSS2	0.754	2.125	0.975	4.630	0.058
CSS3	0.759	2.135	0.661	6.899	0.205
CSS4	-19.569	0.000	0.000	.	0.999
NYHA; NYHA I = 1 as references					
NYHA II	0.399	1.490	0.752	2.953	0.253
NYHA III	1.361	3.898	1.554	9.777	0.004
NYHA IV	23.11	1.093	0.000	.	0.999
Diabetes	-0.123	0.884	0.492	1.590	0.681
Hypertension	-0.123	0.884	0.423	1.848	0.744
Hyperchlolesterolemia	0.193	1.213	0.571	2.576	0.616
Renal Disease	0.897	2.451	1.314	4.570	0.005
Urgency; Elective = 1 as references					
Urgent	0.588	1.800	0.929	3.490	0.082
Emergency	1.967	7.148	1.821	28.058	0.005
Re-Open Location; OT as references					
ICU	0.621	1.860	0.963	3.591	0.064
Bypass time (min)	0.007	1.007	1.003	1.010	0.002
Cross clamp time (Min)	0.009	1.009	1.004	1.020	0.001
Post-op Stay (Day)	0.005	1.005	0.993	1.020	0.405
Renal Failure Need Dialysis	2.788	16.242	8.079	3.270	<0.001
Pulmonary Complication	1.809	6.104	3.123	1.190	<0.001
GI Complication	2.129	8.407	3.366	2.100	<0.001
Heart Failure	2.730	15.34	5.186	4.540	<0.001
Pericardial Effusion	-0.199	0.820	0.438	1.540	0.536
Fever	1.095	2.989	1.487	6.010	0.002
Surgical Site Infection	0.890	2.435	0.931	6.370	0.07

Multivariable Predictors of Mortality
Dependent variable: Mortality

Variable	Univariate Analysis				p-value
	Beta	Odd Ratio (OR)	95% Confidence Interval for Difference		
			Lower Bound	Upper Bound	
Renal failure need dialysis	3.098	22.148	9.160	5.350	<0.001
Heart Failure	1.713	5.545	1.335	2.300	0.018

exploration were minimal as compared to the patients who survived. There was no significant difference between the types of surgery done in the deceased group.

In comparison on the complications developed in the patients involved, ICU vs OT, from the year 2019 to 2020. there were more patients who developed pericardial effusion post-chest re-exploration in ICU group, whereas most patients in the OT group developed fever. It is also portrayed that the patients of the ICU group had higher percentage of complications for all categories than patients who underwent chest re-exploration in an OT, with a significant p-value <0.001.

The time of chest re-exploration for haemostasis in ICU vs OT in deceased patients from 2019 to 2020 was analysed and is shown in Figure 2. The decision for chest re-exploration was predominantly made <12 hours for both the groups, with ICU being the higher percentage as compared to the OT, followed by 24–48 hours, 12–24 hours, and >48 hours, which involved the least percentage of patients who succumbed. The figure also shows the cause of deaths of patients who underwent chest re-exploration for haemostasis (ICU vs OT). The major cause of death in the patients of the ICU group was myocardial failure, whereas sepsis was for those in the OT group. No patient was deceased because of respiratory failure for those who had chest re-exploration for haemostasis in OT, whereas for the ICU group, respiratory failure had the least percentage.

Tables II showed that patients who developed renal failure needing dialysis post-chest re-exploration contributed 16

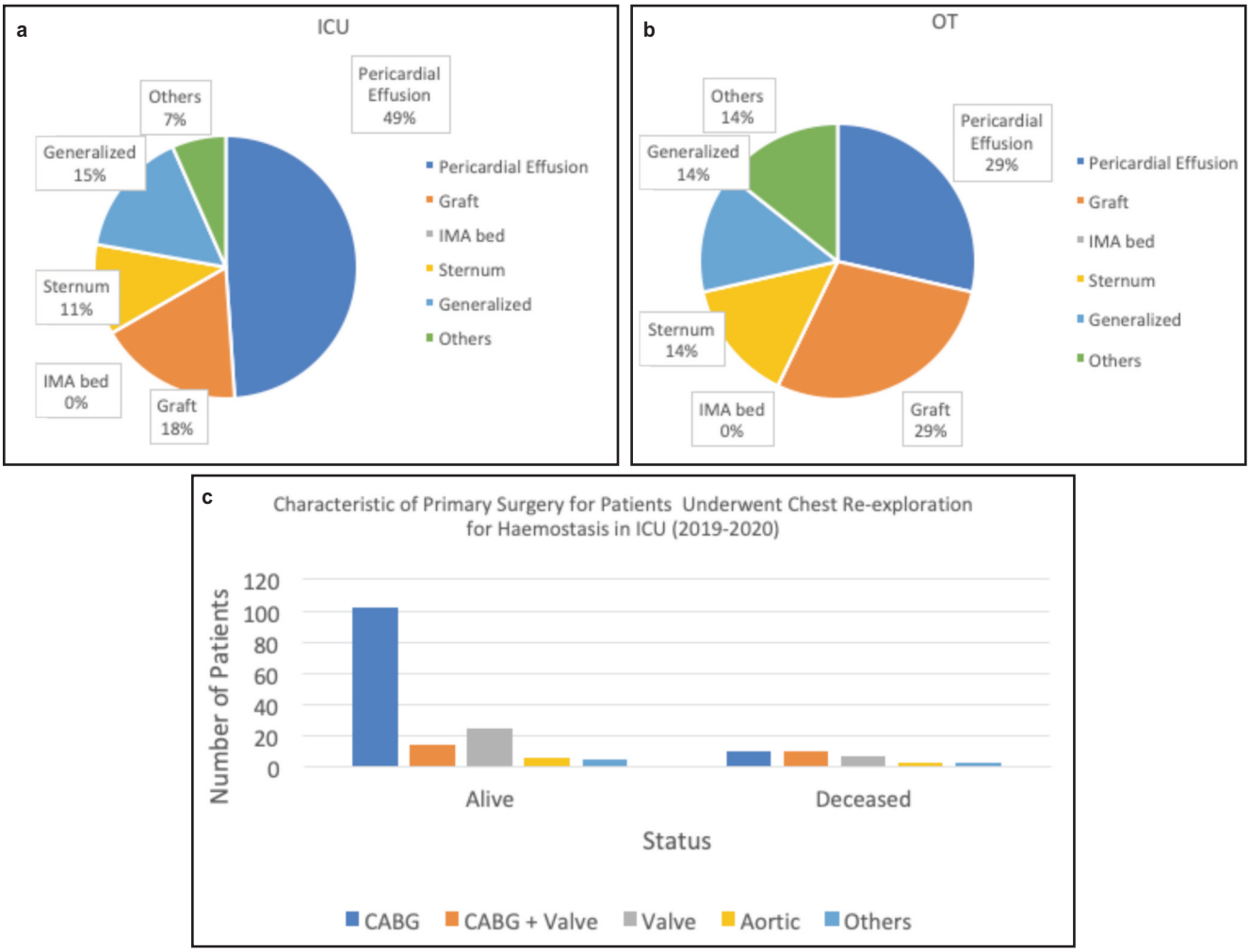

Fig. 1: Source of Bleeding/Tamponade Identified During Chest Re-exploration for Deceased Patients in (a) ICU and (b) OT (2019–2020), & Characteristic of primary surgery for patients who underwent chest re-exploration for haemostasis in ICU 2019–2020.

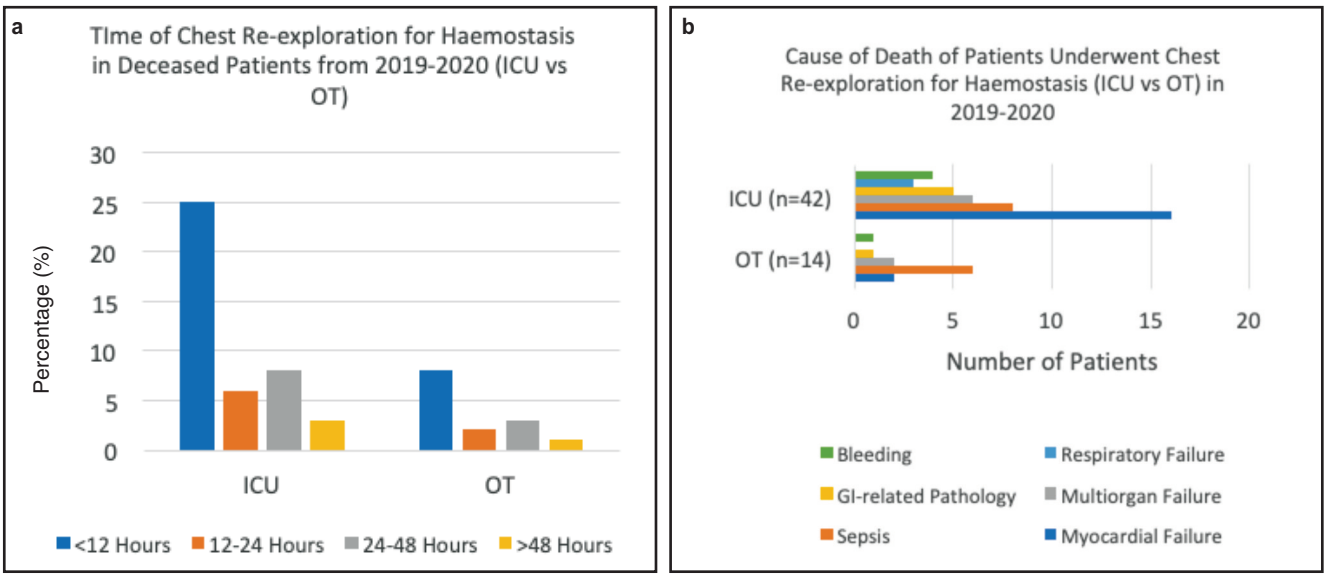

Fig. 2: (a) Time of chest re-exploration for haemostasis in deceased patients from 2019 to 2020 (ICU vs OT) & (b) Cause of death of patients who underwent chest re-exploration for haemostasis from 2019 to 2020 (ICU vs OT).

times towards the mortality rate post-chest re-exploration (OR 16.242, CI [8.079, 3.270], p-value < 0.001). Other complications namely pulmonary complication, GI complication, heart failure, and fever also contributed significantly towards the percentage of mortality post-chest re-exploration.

DISCUSSION

All cases of chest re-exploration for haemostasis were preferred to be conducted in the OT, unless it has to be done immediately, for example, in cases where an active bleeding is suspected, or the patient is hemodynamically unstable to be pushed to the operation theatre, the patient will undergo chest re-exploration in an ICU. From the year 2019 to 2020, 299 out of 4406 cases of open-heart surgery needed chest re-exploration for haemostasis, which accounts to about 6.79%. This percentage is slightly higher than the overall incidence rate of chest re-exploration for bleeding, as reported by Canádyová and Zmeko from Czech Republic, which is about 2.3 to 6%.[2,3-6] This is likely contributed by the fact that our institute is the main cardiothoracic training centre and in comparison to Caucasians, Asians have a higher risk of bleeding, as reported previously.[7]

The results showed that the demographic data and types of primary surgery of patients who underwent chest re-exploration do not contribute significantly towards the patient's outcome. The percentage of death is 8.8% more in patients who underwent chest re-exploration in an ICU rather than an OT, with a p-value of 0.062. Referring to Table 3, all complications showed a higher percentage in those who've had chest re-exploration in ICU as compared to cases conducted in an OT, possibility because of many reasons. Cases of chest re-exploration for haemostasis conducted in an ICU involve patients who are more ill and hemodynamically unstable, for example, suspicion of active bleeding, patients requiring high inotropic support, or any other reasons which disrupt the feasibility of transporting the patient to the OT. Hence, there is high possibility of the involved patients to develop post-operative complications which lead to a higher mortality percentage. Furthermore, an ICU is not a place which is as well-equipped for surgery as compared to an OT, especially in cases which need to be put on cardiopulmonary support in ICU.

There are a few measures that can be taken to improve the outcome of post-chest re-exploration patients, by managing the factors or risk of patients developing complication post-operatively, especially those which are modifiable. We could reduce the risk of bleeding by withholding the anticoagulants in a timely manner as per the guidelines, especially in elective cases. Patients with uncontrolled diabetes, dyslipidaemia and blood pressure should be optimized pre-operatively. To reduce the risk of having pulmonary complication, stable asymptomatic patients who smoke should be given a later date of surgery, where he/she could stop smoking for at least one month. It is also advisable to ensure that the relevant equipment needed for chest re-exploration are complete and reachable in an ICU, to avoid further delay in chest re-exploration or issues during chest re-exploration.

However, with that being mentioned, it is found that the results were not statistically significant, possibly because of the limited sample size and the need to conduct a randomized control trial later. As it is a retrospective analysis, there is also a possibility that biasness is involved.

CONCLUSION

Chest re-exploration in an ICU setting for post-cardiac surgery patients showed a higher percentage of complications, which contributes to a higher percentage of mortality. However, the results are not statistically significant and follow-up study with a bigger sample size, or a randomized control trial is advisable.

ACKNOWLEDGEMENT

We received support from the institute for conducting this study, which was approved by the institutional Ethics Committee.

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ORIGINAL ARTICLE

A survey on workplace violence among pre-hospital care personnel in Malaysia

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ABSTRACT

Introduction: Data on violence experienced by pre-hospital care (PHC) staff in developing countries are lacking. This study investigates incidence, effect, coping reaction, and action taken towards violence received by PHC staff in Malaysia, a developing country.

Materials and Methods: This is a multi-centred cross-sectional survey. Questionnaire modified from the Joint Programme on Workplace Violence in the Healthcare Sector was applied. PHC staff include assistant medical officers, emergency medical technicians (EMTs), nurses, attendants, and ambulance drivers. This questionnaire involves workplace violence (WPV) experienced for 12 months since the beginning of this study among pre-hospital staff of three main hospitals in Klang Valley, Malaysia.

Results: Seventy-one PHC staff personnel responded to this questionnaire. Overall prevalence of at least one WPV incident over past 12 months was 56.3% (95% CI 44.8% to 65.8%). Fifty-three-point-five percent (95% CI 41.9% to 65.1%) experienced verbal abuse, 9.9% (95% CI 3% to 16.8%) experienced physical abuse, and 14.1% (95% CI 6.0% to 22.2%) experienced racial abuse. None of the participants experienced sexual abuse. Out of 38 staff that experienced verbal abuse, 16 (42%) took no action, 8 (21.1%) pretended it never happened, and only 5 (13.2%) filed an actual complaint.

Conclusion: Verbal abuse was found to be the most common type of violence. Younger age group (<29 years) was more exposed to verbal (p = 0.014) and racial abuse (p = 0.007). Majority victims either responded by telling abusers to stop or taking no action at all.

KEYWORDS:
Pre-hospital care, workplace violence, Malaysia, assistant medical officer

INTRODUCTION

Workplace violence (WPV) towards pre-hospital care (PHC) personnel is an alarming phenomenon worldwide.[1] WPV is defined as incident where staff are abused, threatened, or assaulted in circumstances related to their work.[2,3] A study showed that work-related injuries among PHC personnel were three times higher than average for other occupations.[1] This resulted in higher levels of burnout syndrome that includes emotional exhaustion, depersonalisation and lower level of personal accomplishment among PHC personnel when compared to non-healthcare social and administrative counterparts.[4] There are at least two-third of PHC personnel reported in Canada and Australia experiencing WPV within the preceding 12 months,[5,6] while studies done in United States showed up to 93% of PHC personnel reported facing various types of violence throughout their work career.[1] Healthcare worker (HCW) in a public care facility in Italy reported that 1 out of 3 experienced non-physical abuse and 1 out of 10 experienced physical abuse in 2012[7]

Data regarding WPV in Malaysia and developing countries are still scarce and underreported. Furthermore, there is no study done in Malaysia regarding WPV among PHC personnel. Although some measures were taken by the Ministry of Health to control this matter, the incidents are still high and cause negative impact to personnel and organisation.

General objective of this study is to explore violence encountered by PHC personnel in the ground ambulance setting in Klang Valley. Specific objectives were to determine the incident and type of violence involved, effect on PHC staff, coping skills, and action taken to manage the incident. It was hypothesised that there is high incidence of violence experienced by PHC staff in Klang Valley consistent with statistics worldwide. Coping mechanism was expected to be resorted to ignorance.

MATERIALS AND METHODS

Ethical approvement

Ethical approval was obtained from Universiti Kebangsaan Malaysia (UKM) Ethics Committee (Ethical code UKM-ethics committee: FF-2019-091, date of approval: 28/02/2019) for survey done in UKMMC (Universiti Kebangsaan Malaysia Medical Centre). Address for the ethics committee is UKM Research ethical committee, Secretariat of Research and Innovation, Faculty of Medicine UKM, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia. Ethical approval for survey done in other two government hospitals was obtained from Medical Review and Ethics Committee (MREC). Ethical code for MREC: NMRR-18-3816-45146. Address of this committee is National Committee for Clinical Research (NCCR) National

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Pharmaceutical Regulatory Agency, Lot 36, Jalan Universiti, 46200 Petaling Jaya, Malaysia. Study was approved on 26/08/2019.

Study design
This was a multi-centre cross-sectional survey on PHC personnel in three different hospitals in Klang Valley, Malaysia. This study was conducted using modified questionnaire adapted from ILO/ICN/WHO/PSI Joint Programme on Workplace Violence in the Health Sector, Country Case Study Research Instruments.[3] The questionnaire was available in two languages, which were English and Malay, translated and re-translated, and underwent face validation with pre-hospital staff who were not involved in this study.

Investigator approached staff in the PHC unit of each hospital. Explanation was given to participants regarding purpose, risk, eligibility criteria, and benefit of this study. The questionnaires include demographic data and incidence of different types of WPV experienced. Informed and written consent was given by participant before answering the questionnaire.

As the PHC personnel works in shift, investigator had to make a multiple visit at different times to distribute the questionnaire. The approach process stated above was repetitively done on each visit to ensure the understanding of this study for every new subject. Questionnaires that were already been answered were collected instantly by investigator to maintain its confidentiality. Each participant was given some time to complete all the questions immediately. The estimated time to answer all the questions was 30 minutes.

All answered questionnaires from each hospital were collected by the investigator. Once data collection was completed, it was recorded, stored, and analysed in Statistical Package for Social Science (SPSS) Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). No personal information will be published to maintain participant's confidentiality strictly.

Setting
Setting of this study was at pre-hospital unit of Universiti Kebangsaan Malaysia Medical Center (UKMMC), Hospital Tengku Ampuan Rahimah, Klang (HTAR), and Hospital Kuala Lumpur (HKL), Malaysia. Survey was conducted for 3 months from 1st of June to 31st August, 2019.

Eligibility criteria
All PHC staff, including assistant medical officer (AMO), nurse, and ambulance driver from the three different hospitals, were included in this study. Participants were actively working in the PHC units taking ambulance calls for the past 12 months. Unreturned or incomplete questionnaire was excluded from the study. Method of selection was based on convenience sampling. Each participant had to answer all the questionnaires within 30 minutes. Assistant medical officer role.[8]

Pre-hospital medical assistant practice is in accordance with nationally accepted standards: a) initial assessment of patients and immediate intervention deemed necessary where relevant such as triaging of patients for emergency services and PHC patients; b) administering treatment and performing procedures as ordered by the medical practitioners via online or offline medical direction; c) reviewing and reporting changes in the progress of the patient where relevant; d) completing the planned management with proper documentation.

PHC medical assistants shall be trained in basic life support (BLS) within 2 months after being placed in the emergency services. All medical assistants in the emergency services shall continuously participate in Advanced Life Saving and Trauma Programme (Malaysian Trauma Life Support [MTLS]/Advanced Trauma Life Support [ATLS]/Advanced Cardiac Life Support [ACLS]/Pediatric Advanced Life Support [PALS]) or any advanced programme done by emergency services within 2 years after being placed in the emergency services.

Emergency medical technician (EMT) is the minimum licensure level for personnel transporting patients in ambulances. The scope of practice is limited to basic skills that are effective and can be performed safely in an out-of-hospital setting with medical oversight and limited training. Usually, an attendant is employed and given basic training such as BLS. An EMT has the skills to assess a patient's condition and to manage respiratory, cardiac, and trauma emergencies. Furthermore, advanced management will be passed over to the AMO, which is equivalent to a paramedic. EMT in this study is equivalent to an EMT basic level in the United States. EMT unfortunately is only available in PPUKM, a teaching hospital, whereas in other hospitals EMT does not exist, and role is replaced by AMO and medical attendant. This explains the grouping of AMO/EMT/medical attendant into one category.

The pre-hospital nurse provides nursing care and functions under the direction of an administrative base hospital, which is the head of nursing, and emergency physician through policies, procedures, medical protocols, and/or standing orders to maintain appropriate and effective levels of care for the patient. Nurses in PHC PPUKM is mainly midwifery, a health professional trained to support and care for women during pregnancy, uncomplicated labour and birth at the pre-hospital setting. Nurses are from the obstetric unit that connects directly with the pre-hospital unit when responding to calls from a patient who is in labour.

Variables
Outcome from the survey is to determine incidence of WPV among PHC personnel in Klang Valley (Malaysia). Other outcomes are to establish the impact of WPV towards coping mechanism and response.

The questionnaire consists of two major sections: demographic data and physical and psychological violence experienced by the PHC personnel. The psychological violence includes verbal, bullying/mobbing, and sexual harassment. Each type of violence was arranged in various colour codes. Red colour was coded for physical violence, blue was coded for verbal abuse, yellow was coded for bullying/mobbing, green was coded for sexual harassment,

Table I: Sociodemographic distribution of respondents

Variables	Frequency (N = 71)	Percentage (%)
Age:		
20–29	23	32.4
30–39	41	57.7
40–49	4	5.6
50–59	3	4.2
Gender:		
Male	65	91.5
Female	6	8.5
Race:		
Malay	65	91.5
Chinese	3	4.2
Indian	2	2.8
Others	1	1.4
Marital status:		
Single	14	19.7
Married	57	80.3
Professional group:		
AMO/EMT	51	71.8
Nurses	4	5.6
Drivers	16	22.5
Years of experience:		
1–5 years	27	38.0
6–10 years	26	36.6
11–15 years	16	22.5
More than 20 years	2	2.8

Table II: Breakdown of violence experienced and witnessed by PHC staff in Klang valley for past 12 months

	Physical Attack	Verbal Abuse	Bullying/ Mobbing	Sexual Harassment	Racial Harassment	Total
Types of violence experienced	7 (11.5%)	38 (62.3%)	6 (9.8%)	0 (0%)	10 (16.4%)	61
Types of violence witnessed	18 (20.7%)	42 (48.3%)	9 (10.3%)	3 (4.2%)	15 (21.1%)	87
Occurrence of violence witnessed						
Once a month	17 (33.3%)	17 (33.3%)	8 (15.7%)	2 (3.9%)	7 (13.7%)	51
Few times/month	1 (4.8%)	12 (57.1%)	1 (4.8%)	1 (4.8%)	6 (28.6%)	21
Every week	1 (25%)	2 (50%)	0	0	1 (25%)	4
Near daily	1 (7.8%)	11 (84.6%)	0	0	1 (7.8%)	13
Perpetrator profile						
Patient	5 (13.5%)	24 (64.9%)	2(5.4%)	0	6 (16.2%)	37
Patient's relatives	5 (15.2%)	19 (57.6%)	3(9.1%)	0	6 (18.2%)	33
Public	5 (11.1%)	30 (66.7%)	4 (8.9%)	0	6 (13.3%)	45
Colleague	0	2 (25%)	4 (50%)	0	2 (25%)	8
Supervisor		3				3
Victim profile						
Assistant medical officer	6 (11.5%)	32 (61.5%)	5 (9.6%)	0	9(17.3%)	52
Nurses	0	4 (66.7%)	1(16.7%)	0	1(16.7%)	6
Drivers	1 (33.3%)	2 (66.7%)	0	0	0	3
Place of incident						
At response scene	4	25	4	0	4	37
In ambulance	3	10	2	0	1	16
In hospital/institution	6	29	4	0	8	47

Table III: Individual responses towards each type of violence experienced

Victim's reactions	Physical Attack	Verbal Abuse	Bullying/Mobbing	Sexual Harassment	Racial Harassment
Took no action	1 (8.3%)	16 (22.5%)	2 (25%)	0	2 (10.5%)
Pretend it never happened	1 (8.3%)	8 (11.3%)	2 (25%)	0	4 (21%)
Asked the person to stop	4 (33.3%)	18 (25.3%)	0	0	6 (31.6%)
Told family/friends/colleagues	2 (16.7%)	11 (15.5%)	2 (25%)	0	4 (21%)
Report to senior staffs	3 (25%)	11 (15.5%)	1 (12.5%)	0	1 (5.2%)
Sought counselling	0	1 (1.4%)	0	0	0
File incident reporting	1 (8.3%)	5 (7%)	0	0	2 (10.5%)
Others	0	1 (1.4%)	1 (12.5%)	0	0

Note: frequency, n (%)

and orange was coded for racial harassment. The definition of each type of violence was adopted from ILO/ICN/WHO/PSI and included in the questionnaire.

RESULTS

This questionnaire involves WPV experienced by pre-hospital staff in three main hospitals in Klang Valley, Malaysia, for past 12 months. Seventy-one pre-hospital staff personnel responded to this questionnaire, and the overall prevalence of at least one WPV incident over past 12 months was 56.3% (95% CI 44.8% to 65.8%). Fifty-three-point five percent (95% CI 41.9% to 65.1%) experienced verbal abuse, 9.9% (95% CI 3% to 16.8%) experienced physical abuse, and 14.1% (95% CI 6.0% to 22.2%) experienced racial abuse. None of the participants experienced sexual abuse. Out of 38 staff that experienced verbal abuse, 16 (42%) took no action, 8 (21.1%) pretended it never happened, and only 5 (13.2%) filed an actual complaint. Verbal abuse was found to be the most common type of violence. Younger age group (<29 years) was more exposed to verbal (p = 0.014) and racial abuse (p = 0.007). Victims are bothered by the incident's majority responded by telling them to stop.

Demographic characteristics

Total staff of PHC units in the three centres were 118. Ninety questionnaires were distributed. Out of this total number of samples, only 71 participated, as of a number of staff were transferred to different units, did not fulfilled inclusion criteria, or did not complete the form due to failure to recall incidents within one year. Three did not complete (missing data) and 16 did not return the questionnaire. Demography of the respondents is shown in Table I.

Factors contributing towards violence

Younger age (20–29 years old) was found to be a significant factor that contributed to verbal abuse (p = 0.014) and racial harassment (p = 0.007) (Pearson chi-square). Other factors were not significant in contributing towards violence experienced by respondents.

There is no significant difference among working groups who experienced physical attack, bullying, and racial harassment. In addition, working experience was also found to have no significant different towards the incident of violence in all types. Another factor contributing towards violence is location. Majority incidents of all types of violence experienced occurred either at scene or in the hospital compound (Table II).

Effects of physical violence towards PHC personnel

The effect of WPV towards individual personnel was explored in terms of physical injuries and psychological health impacts. Among seven respondents who experienced the physical attack in 12 months, only one respondent who sustained injury, whereas two of them (29%) needed 'time off' from work for 2–3 days. Most of these respondents (71.4%) could not recall the day of incident but the attacks were found to be common within 1300 to 1800 hours (71.4%).

Response towards violence

In this part, individual and systematic responses towards violence are explored. Individual response includes coping strategies among victims, while systematic response includes reporting procedure and intervention done towards violence experienced. Table III summarises individual responses to each type of violence.

DISCUSSION

This is the first study on abuse of PHC staff in Malaysia. A significant number (N = 71) of respondents were obtained from the three hospitals in Klang Valley. High prevalence of WPV among PHC personnel was expected. Fifty-six percent respondents reported at least one type of violence in the past 12 months. Percentage of PHC personnel experienced any types of violence in the past 12 months was lower than previously reported elsewhere. For instance, this Malaysian survey of WPV was lower than other middle-/low-income countries such in India, where the prevalence was 67.9%.[9] Our study also revealed significantly lower WPV than reported by EMTs in Australia and Sweden where more than 80% had first-hand experience during the past 12 months.[10,11]

A number of factors associated with increased likelihood of violence were identified. Younger age is associated with higher exposure to violence as reported by Gormley et al. and Kasara et al.[1,12] Younger age group has significant correlation with higher incident of verbal abuse.[12] In this study, the younger age group (<29 years) was more exposed to verbal (p = 0.014) and racial abuse (p = 0.007). In this study, however, there was no significant correlation on abuse incidence between shorter working experience (less than 5 years) in comparison to longer working experience (more than 10 years). This is a stark contrast when compared to previous studies where personnel who have working experience of less than 5 years has higher incident of violence.[1,12] Age does not correlate directly to working experience, as some staff might have started later in the pre-hospital workforce from others.

Although more than 90% of respondents in this study were males, all female respondents were found to experience at least one of any type of violence. This was also observed in other studies, in which females were reported having higher prevalence to violence[1,5] The more common perpetrator of violence reported are patient's relative, patient himself, and public observed. These findings are akin to several other studies observed.[3,13] In fact, there are a several types of acts of violence that were committed by two or more perpetrators. Nevertheless, none of our respondents had reported of having encountered any sexual harassment in the past 12 months.

In various studies worldwide, an AMO/EMT has higher exposure to violence in comparison to driver, nurses, or attendant[3,14] It is similar to this study; however, there is a bias effect since majority of respondents consist of AMO/EMT.

In this study, race and marital status did not show any significant different to the likelihood of violence to occur. These findings are similar to the study done by Kasara et al.[12] where ethnicity and marital status in a country like Thailand also did not show any significant value when compared to any types of violence. However, the ethnic breakdown of the participants was also skewed in which 91.5% are Malay.

Verbal abuse was found in this study to be the most common type of violence (53.5%), consistent with most of the literature reports elsewhere.[5,12,14] Verbal abuse is a known hazard for healthcare-related personnel.[15] Kasara et al.[12] found that the most common perpetrator for verbal abuse was by colleagues or staff members. In contrast to study done by Kasara et al., this study showed no significant different between places of incident on any types of violence. A study on pre-hospital paramedic personnel in Iran in 2019 showed 47% out of 308 respondents faced verbal assault.[16] Verbal assaults towards PHC personnel are not uncommon and occur mostly at the emergency site.[17] However, our study revealed that verbal assaults towards paramedics occur in hospitals and could be delivered by hospital personnel. Overcrowding in emergency departments has become worldwide problem, which affected the location of study.[18] Heavy workload and emergency department overcrowding could increase verbal assault among colleagues of same fraternity due to being held in departments for prolonged periods and unable to transfer care to the respected hospital staff.[10,19,20]

Physical attack (9.9%,95% CI 3% to 16.8%) in this study was lower than reported in metropolitan regions in developed countries.[15,17,21] It was reported in 1998 that emergency medical services providers in a southern California metropolitan area on out of 490 samples analysed, 61% recounted assault on the job throughout working experience, with 25% reporting injury from the assault. Respondents reported a median of three episodes, and the number of assaults for each individual was unrelated to the number of years of experience on the job (r = 0.068). Of those injured, 37% required medical attention.[21] It was often described that people of Asian background have tendencies to avoid confrontation and conflict.[22] According to the data gained from this study, the connotation still holds in Malaysia as compared to other Asian countries.[9,23,24] Strict firearm control and heavy punishment in illegal firearms possession in Malaysia might have contributed to this result.[25] High number of physical abuse reported in Swedish ambulance (16% for the past year) is associated with drug and alcohol abuse.[26] This can be translated with lower incidence of alcohol-/drug-related violence experienced by our pre-hospital staff.

It is observed in this study that the most common response towards physical violence and verbal abuse is 'telling the perpetrator to stop'. Other common responses, including 'pretending that nothing happened', 'telling other family members or friend', and even 'taking no action' against the violence, were reported. These findings are quite similar to other similar studies done. Less than 10% of incident of violence were actually filed with incident reporting, similar to a study done by Alharthy N (2017).14 Daniela et al.[13] reported that only one third of volunteers and HCW who were victims of psychological and physical abuse reported to higher authorities.

Implications for policy, practice, and research

Abuse towards PHC is prevalent in developing countries. According to this study, verbal abuse consists of majority endured by the staff. In Malaysia and across much of the world, there is lack in specialised training on how to manage WPV and safety threats. Most respondents did not receive any training on how to deal with such incidents.

Few steps for improvement can be considered in improving facing and reaction to abuse. First is the knowledge of special populations, sensitivity, and attitude of different socioeconomic conditions in a multiracial Malaysia. Multiple webinars and tutorials with experts in the field can assist. Second is the ability to restrain or defend oneself from abuse, especially physical and sexual abuse. De-escalation technique should be applied, rather than training each PHC staff with self-defence, improving social soft skills would be more beneficial and cost effective. Third is developing systems for advanced warning about potentially violent patients in liaison with police and law enforcers. Collaboration with other public or private EMT in detecting hot zones is crucial in order to take precautionary steps when responding to scene.[9]

These results show limited research to date, suggesting that a much broader effort is required to address workplace safety and violence among EMTs. Pathways for improved recognition and reporting of WPV are required. Specialised training programme for EMTs on dealing with WPV would be extremely beneficial. Finally, EMTs should be covered by regulations and/or policies to protect HCWs. Access to counselling facilities is limited, and administrators need to acquire more encouragement in this aspect.

LIMITATIONS AND RECOMMENDATIONS

The main limitation of this study is that it adopts a small convenience sample size. There is high incident of selection bias. The sample size counted earlier was 90, of which only 71 respondents were accepted. This is because, in most of healthcare settings, the number of staffs for PHC unit was estimated roughly since the exact number of each professional group was keep changing. Since some of the staffs were transferred to other department/ hospital and some went for post-basic programme, these staffs may be replaced by new staffs or recruited from other department/hospitals. Therefore, the number of personnel that fulfilled the inclusion criteria of actively working in the past 12 months was reduced. Furthermore, almost 10% of questionnaires distributed were not returned. It was also observed that some of the returned questionnaires were not fully answered. There is the possibility of information bias, as personnel may not have been able to recall all instances of violence occurring over the past 12 months.

The sampling method was convenience sampling; hence, there is potential bias of under-representing the population of PHC staff throughout Malaysia. Data of population is skewed in terms of race, gender, and professional group. Males are widely represented, while in health professions around the world, and even in Malaysia, females are in the majority. However, for pre-hospital staff, including paramedics, AMOs, and drivers, male gender still represents the majority of responders. Thus, exact data for Malaysian PHC staff is not available.

Another limitation is that AMO and EMT were grouped under one category due to inconsistent definitions and work scope throughout different hospitals. For example, in PPUKM, EMT is employed among SPM leavers and attendants who have undergone BLS training, whereas the definition of EMT does not exist in KKM hospitals, where the hierarchy is senior

AMO, AMO, and medical attendant.[27] As the work scope differs from each hospital, hence the sample category for EMT will be small if separated from the others. The results of this study cannot be generalised as representing the whole population in Malaysia, as other confounding factors are present such as rural/urban areas and areas with different race/sociodemographic distribution. As many of them are affected, education and support group should be provided to those identified as high risk for WPV. As the study was done before the pandemic, the similar study should be conducted during or post-pandemic era to assess the WPV.

CONCLUSION

This study raises awareness to the prevalence of violence among PHC personnel in Malaysia and the factors associated with the violence experienced. Verbal abuse was found to be the most common type of violence among PHWC personnel. It was found that among our respondents, AMO/EMT had a significant higher incident of abuse. Age was a significant factor towards abuse, whereby age of 29 years or younger were the most susceptible. Victims were found to be bothered by the incidents, but the majority responded by only telling family and friends or asked the abuser to stop, while others did not take any action against the abuser.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING DETAILS

This research received no funding.

CONSENT

Consent has been obtained from participants for the questionnaire. Consent and information for participants are provided in the appendix.

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ORIGINAL ARTICLE

Factors influencing the psychosocial impact of COVID-19 pandemic on healthcare workers and their level of satisfaction towards organisational efforts

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ABSTRACT

Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic has had a dramatic physical, personal, and emotional effect on healthcare workers (HCWs). The main objective of this study was to identify risk factors associated with psychosocial distress among HCWs working in a hospital environment during the pandemic.

Materials and Methods: A cross-sectional descriptive survey involving HCWs of a tertiary care hospital was completed using an online survey software (Google Forms). The survey collected respondents' sociodemographic data, perception towards personal protective equipment (PPE) and knowledge about COVID-19, and satisfaction score towards performance of the World Health Organization, the Malaysian police, civil service, healthcare system, and government. Psychosocial distress was assessed using the 12-item version of the General Health Questionnaire (GHQ-12).

Results: A total of 675 responses were collected. Female gender and doctors were identified to be associated with greater psychosocial impact from the pandemic among the HCWs. Several factors such as self-rated health status, confidence level towards PPE in disease prevention, degree of familiarity in using PPE, knowledge regarding care for COVID-19 patients, and capability in answering questions asked by the public regarding the disease were found to be associated with the degree of psychosocial impact from the pandemic.

Conclusion: This study identified the vulnerable groups of HCWs at risk of psychosocial distress and its associated risk factors. These findings highlight the need for strategies to reduce risks and to prioritise psychological support and intervention during the pandemic.

KEYWORDS:
Psychosocial factor, COVID-19, Healthcare workers

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) is the largest outbreak of atypical pneumonia since the severe acute respiratory syndrome (SARS) outbreak in 2003. It was first revealed in late December 2019, but later declared as a pandemic and a global health threat by the World Health Organization (WHO) on 11th March, 2020, as the number of confirmed cases had risen exponentially around the world.[1]

The Federal Government of Malaysia implemented the 'movement control order (MCO)' as a preventive measure on 18th of March, 2020.[2] The order involves a general prohibition on mass movement and gatherings across the country. Additionally, a range of measures have been implemented – including prohibition of sporting, religious, social, and cultural activities; closure of all kindergartens, schools, institutions of higher education, and skills training institutes; closure of all business premises except for supermarkets, public markets, and grocery or convenient stores selling essential goods; and the closure of all government and private premises except for those involved in essential services.[2,3] For premises that were allowed to operate, they were required to follow strict standard operating procedures set by the authorities.[2,3] The MCO was finally relaxed on 4th May, 2020, with a 'conditional MCO (CMCO)' implemented, which allowed certain business sectors to resume operations.[4] The CMCO was followed by 'recovery MCO' from 10th June until 31st August, which allowed 'almost all' social, educational, religious, and business activities, as well as economic sectors to reopen in phases while adhering to standard operating procedures.[5] Our study period coincided with the transition from CMCO to recovery MCO.

Sarawak General Hospital (SGH) is a tertiary care state hospital with 1005-bed capacity. It is one of the hospitals in Ministry of Health of Malaysia designated for admitting patients with suspected COVID-19 termed as 'Person Under Investigation (PUI)' and confirmed COVID-19 infection. Since the beginning of the pandemic, several infection control directives have been implemented. There was a reduction of

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patient caseload for outpatient clinics, endoscopy services, and elective operating theatre. The entry into hospital for patients and staff had been limited to certain entrances with mandatory temperature reading, symptoms/exposure checking through questionnaire, and scanning of the MySejahtera web app. Hospital staff were required to wear surgical masks at all times.

Healthcare workers (HCWs) working in hospitals caring for patients with suspected or confirmed COVID-19 infection are at high risk of nosocomial spread. There have been reports of high rates of infection and even death from COVID-19 among HCWs.[6] Given the magnitude of the pandemic, coupled with the high physical and mental demands in performing duties, it is not unexpected that adverse psychological outcomes occur among HCWs. Medical HCWs who were directly involved in diagnosis, treatment, and care of patients with COVID-19 were reported to have a higher prevalence of psychosocial problems compared with nonmedical HCWs.[7] Among the psychological impact reported were depression, anxiety, insomnia, somatisation, obsessive-compulsive symptoms, acute stress symptoms, emotional distress, burnout, stigmatisation, and post-traumatic stress symptoms.[7-13] The psychosocial outcomes caused by an outbreak of infectious disease are influenced by a variety of factors. The constant changes in infection control policy and procedure in response to evolving understanding of the disease cause confusion and anxiety among the HCWs. Other stressors include infection-related fears, the ever-increasing number of confirmed and suspected cases, depletion of personal protective equipment (PPE), overwhelming workload, lack of treatment response drugs, stigmatisation, and widespread media coverage.[7-10] Until now, little is known about the psychosocial impact of the COVID-19 pandemic on HCWs in Malaysia.

With the current focus of the health authorities mainly on prevention, management, and limitation of the spread of COVID-19, it is important to evaluate how both the pandemic and the strategies adopted to deal with it have impacted the psychosocial well-being of the HCWs and identify factors that are associated with psychosocial distress, so that the necessary steps can be taken to mitigate the problems.

MATERIALS AND METHODS

Study design

This study was a cross-sectional, online survey conducted from June 1st to June 13th, 2020. The survey was performed using Goggle Forms, and the link to access the survey was distributed via WhatsApp messages to all willing employees (both medical and non-medical HCWs) who worked at SGH. Participation in this survey was voluntary and consent was obtained prior to the start of the survey. The participants must have a legal capacity to consent and be able to read and understand written English. Participants who had been diagnosed to have a psychiatric illness or unable to complete the questionnaire were excluded from the study. Institutional approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health of Malaysia prior to commencement of the study (NMRR-20-1271-55333).

Questionnaire

The survey consisted of questions categorised into four main sections: sociodemographic, 12-item version of the General Health Questionnaire (GHQ-12), knowledge and confidence level towards PPE, and the degree of satisfaction towards the performance of specific organisation and service provider. The first section gathered information on the age, gender, ethnicity, education level, marital status, underlying chronic medical illnesses, previous diagnosis of COVID-19, occupation, workplace, employment status, and tenure of the respondents. The second section assessed the psychosocial well-being of the respondents using GHQ-12. It is the shortest version of the original 60-item questionnaire (GHQ-60) and is particularly useful when used in busy clinical settings. It has been widely used in many countries as a screening tool to detect psychological morbidity.[14,15] It consists of 12 items, each one assessing the severity of a mental problem over the past few weeks using a bi-model scale (0-0-1-1) or a 4-point Likert-type scale (from 0 to 3). The 4-point Likert-type scale was used in this study because it produces a more acceptable distribution of scores for parametric analysis with less skew and kurtosis.[15] The total score generated ranges from 0 to 36, with higher score indicating worse mental health.[16] Previous studies revealed that the GHQ-12 should be considered as multidimensional instrument as it contains three factors, which are anxiety and depression, social dysfunction, and loss of confidence,[14,15] and is capable of assessing several distinct aspects of distress.[17] The third section measured the self-rated health status, from very poor to excellent. Additionally, respondents were asked about their perception towards sufficiency of PPE in their workplace; their confidence level in PPE; adequacy of knowledge regarding care of COVID-19 patients; and their capacity in answering questions asked by public regarding the disease. For perception of sufficiency of PPE in workplace, the respondent should mark one answer from the options yes, no, or don't know. The rest of the questions were assessed using a five-point Likert score (from 1 [very low] to 5 [very high]). The fourth section measured the degree of satisfaction towards performance of the Malaysia's police, Malaysia's civil service, Malaysia's healthcare system, World Health Organization (WHO), and Malaysia's government, with a scoring system of 0 to 10 used (zero signified the worst score, while 10 signified the best score).

Sample size calculation

The target sample size of participants was determined using the formula $n = [z^2 * p * (1 - p) / e^2] / [1 + (z^2 * p * (1 - p) / (e^2 * N))]$, in which z = 1.96 for a confidence level of 95%; p = proportion (expressed as a decimal); N= population size of HCWs in Sarawak General Hospital; e = margin of error.
Z = 1.96, p = 0.5, N = 5328, e = 0.05

For this cross-sectional study, researcher must examine at least 359 completed questionnaires from participants.

Statistical analysis

Data were analysed using IBM SPSS Statistics V.21. (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Descriptive statistics were presented to describe the demographic profile of the respondents and other parameters. Independent sample t-test

Table I: Respondents' demographic characteristics and association with total GHQ-12 scores

Variables	N (%)	Total GHQ-12 Score	
		Mean score (SD)	p-value
Gender			
Male	160 (23.7)	16.98 (6.16)	0.017
Female	515 (76.3)	17.05 (5.17)	
Age (Years)			
21-30	309 (45.8)	17.50 (5.51)	
31-40	238 (35.3)	16.97 (5.52)	0.212
41-50	106 (15.7)	16.46 (4.69)	
51-60	22 (3.3)	13.86 (5.41)	
Ethnicity			
Malay	210 (31.1)	16.99 (5.08)	
Chinese	180 (26.7)	18.20 (5.09)	0.638
Sarawak native	239 (35.4)	16.31 (5.66)	
Others[a]	46 (6.8)	16.43 (6.26)	
Education level			
Primary/ Secondary education	110 (16.3)	15.29 (4.79)	
Bachelor's degree or diploma	524 (77.6)	17.27 (5.41)	0.274
Master's degree and above	41 (6.1)	18.61 (6.20)	
Marital status			
Single	255 (37.8)	17.44 (5.53)	
Married	394 (58.4)	16.84 (5.24)	0.093
Divorced/Separated/ Widowed	26 (3.9)	16.00 (6.78)	
Hypertension			
Yes	47 (7.0)	15.45 (4.32)	0.524
No	628 (93.0)	17.15 (5.48)	
Diabetes			
Yes	19 (2.8)	15.26 (6.67)	0.695
No	656 (97.2)	17.08 (5.38)	
Hyperlipidaemia			
Yes	43 (6.4)	17.65 (5.72)	0.091
No	632 (93.6)	16.99 (5.40)	
Asthma			
Yes	57 (8.4)	18.16 (6.45)	0.098
No	618 (91.6)	16.93 (5.31)	
History of COVID-19			
Yes	37 (5.5)	16.97 (6.46)	0.414
No	638 (94.5)	17.03 (5.36)	
Occupation			
Allied health care professional[b]	46 (6.8)	17.72 (6.99)	
Non patient-care occupation[c]	59 (8.7)	15.61 (5.17)	<0.001[A]
Nurse/ Medical assistant	350 (51.9)	16.11 (4.86)	
Doctor	220 (32.6)	18.74 (5.54)	
Work place			
Administration	42 (6.2)	15.69 (5.90)	
Operating theatre (major)	81 (12.0)	18.94 (4.90)	
Emergency department	50 (7.4)	17.88 (4.31)	0.244
Hospital adult in-patient ward	363 (53.8)	16.75 (5.47)	
Hospital out-patient clinics	115 (17.0)	16.42 (5.40)	
Others[d]	24 (3.6)	18.38(6.12)	

SD means standard deviation
[a] Indian, Sabahan, or other races not specified
[b] Social workers, pharmacists, medical imaging technologists, physiotherapists, dietitians, audiologists and respiratory therapists
[c] Administration, food services, maintenance and research
[d] Endoscopy suites, daycare operating theatre, radiology department or other places not specified
[A] Post-hoc analysis was done for significant result to identify the association among subgroups. The outcome of analysis was mentioned in the "result" part.

and one-way Analysis of Variance were used to determine the association between potential predictor towards GHQ score. Then, a multivariate analysis using General Linear Model Analysis of Co-variances was used to assess the association between potential set of associated factors towards GHQ score. A p-value of less than 0.05 is considered statistically significant.

RESULTS

There were 685 responses to the survey. Ten were excluded in view of pre-existing psychiatric illness. The remaining 675 responses were further analysed. Table I shows the sociodemographic characteristics of the respondents and their association with total GHQ-12 scores. The largest percentage of respondents was women (76.3%), aged 20 to 30 years (45.8%), Sarawak native (35.4%), well educated (83.7%

Table II: Association between self-rated health status, PPE and knowledge during COVID-19 outbreak with total GHQ-12 scores

Variables	N(%)	GHQ-12	
		Mean score (SD)	p-value
Self-rated health status			
Good to excellent	515 (76.3)	16.51 (5.18)	
Fair	144 (21.3)	18.65 (5.06)	<0.001
Poor to very poor	16 (2.4)	19.25 (10.82)	
Perception towards sufficiency of PPE in workplace			
Yes	309 (45.8)	16.24 (4.86)	
No	226 (33.5)	17.94 (6.07)	0.175
Don't know	140 (20.7)	17.31 (5.25)	
Confidence level towards PPE in disease prevention			
Low to very low	40 (5.9)	20.65 (5.63)	
Moderate	318 (47.1)	17.25 (5.00)	<0.001
High to very high	317 (47.0)	16.35 (5.61)	
Degree of familiarity in using PPE			
Low to very low	37 (5.5)	20.41 (6.03)	
Moderate	301 (44.6)	17.39 (5.14)	0.001
High to very high	337 (49.9)	16.34 (5.44)	
Adequacy of knowledge regarding care for COVID-19 patients			
Low to very low	80 (11.9)	19.01 (5.82)	
Moderate	354 (52.4)	17.35 (5.27)	0.004
High to very high	241 (35.7)	15.90 (5.26)	
Capability in answering questions asked by public regarding the disease			
Low to very low	51 (7.6)	20.29 (6.29)	
Moderate	378 (56.0)	16.85 (5.08)	0.001
High to very high	246 (36.4)	16.63 (5.53)	

Note: Each of the question were analysed independently and the results were derived after control for sociodemographic data such as age, gender, ethnicity, education level, marital status, hypertension, hyperlipidaemia, asthma, diabetes, work place, occupation group, and history of diagnosed to have COVID-19 in the analysis

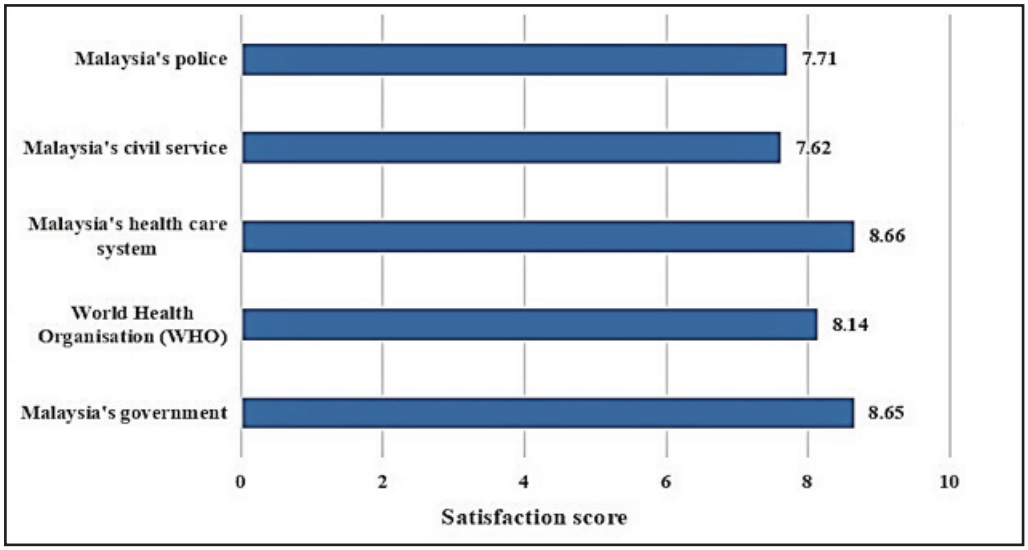

Fig. 1: Satisfaction score towards the efforts of each organisation in handling the COVID-19 outbreak.

≥ bachelor's degree or diploma), married (58.4%), without chronic illness (68.3%), without history of COVID-19 infection (94.5%), nurses or medical assistants (51.9%), and worked in the adult in-patient ward (53.8%). Almost all respondents reported full-time employment status (99.0%), and 71.0% (479/675) of them stated that they had worked 4 or more years in their current occupation.

Sociodemographic characteristics and total GHQ-12 score

The mean score for GHQ-12 among 675 respondents was 17.03 (SD 5.42). There was a statistically significant difference of the mean score for gender (p=0.017) and different occupation group (p<0.001). Mean score was higher for female HCWs (17.05 SD 5.17), compared to male HCWs (16.98 SD 6.16). Doctors had the highest total GHQ-12 score among all HCWs, followed by allied healthcare professionals, nurses/medical assistants, and non-patient-care occupation workers. Post-hoc analysis showed that there is statistical significance between doctor vs. non-patient-care occupation workers (p<0.001) and doctor vs. nurses/medical assistants (p<0.001). The pairing of allied healthcare professionals and non-patient-care occupation workers also showed significant difference in mean score (p=0.041).

Self-rated health status, PPE, and knowledge influencing the total GHQ-12 score

The association between self-rated health status, PPE, and knowledge about the disease with the total GHQ-12 score is shown in Table II. There were 515 (76.3%) respondents who rated their health as good to excellent, 144 (21.3%) as fair, and 16 (2.4%) as poor. Less than half (45.8%) of the respondents perceived PPE as sufficient. A large majority of patients expressed moderate to very high confidence level towards PPE in disease prevention (n=635, 94.1%), familiarity using PPE (n=638, 94.5%), and capacity in answering questions asked by the public (n=624, 92.4%). Most expressed moderate to very high adequacy of knowledge regarding care for COVID-19 patients (n=595, 88.1%). The analysis indicated that a poorer self-rated heath status was associated with a significant higher GHQ-12 score (p<0.001), whereas increasing confidence level (p<0.001) and degree of familiarity with PPE (p=0.001), increasing knowledge of care for COVID-19 patients (p=0.004), and higher capacity in answering questions regarding the disease (p=0.001) were significantly associated with a lower GHQ-12 score. Perception towards sufficiency of PPE in workplace did not significantly influence the score (p=0.175).

Satisfaction score in handling COVID-19

Satisfaction score towards the efforts of each organisation in handling the COVID-19 outbreak was rated on a scale of 0 to 10 by HCWs (Figure 1). Malaysia's healthcare system scored the highest (8.66), followed by Malaysia's government (8.65), WHO (8.14), Malaysia's police (7.7), and lastly Malaysia's civil services (7.62).

DISCUSSION

This study aimed to identify factors associated with psychosocial distress during the COVD-19 pandemic among HCWs. It assessed the perceived psycho-social impact of several factors (sociodemographic, workplace, health-related, perception-related, and knowledge-related) on HCWs of a tertiary hospital. The main characteristics of the respondents were of age ≤ 40 years (81.1%), female gender (76.3%), of education level at least a bachelor's degree or diploma (83.7%), married (58.4%), and without chronic illnesses (68.3%). Majority of the respondents (84.5%) were either nurses, medical assistants, or doctors. More than half (53.8%) of the respondents worked in adult in-patient wards, and 37 (5.5%) of them had previous diagnosis of COVID-19 infection.

This study identified female gender as one of the sociodemographic factors found to have significantly higher psychosocial impact from the pandemic. There are gender differences in expression of emotions in adults, with women showing greater emotional expression than men.[18] During the pandemic, women were found to be at a higher risk of experiencing depression and anxiety.[7,12,19] However, it is noteworthy to mention that female respondents were over-represented in most studies involving general teaching hospitals or tertiary care hospitals.[20] In our study, female participants represented 76.3% of the respondents, and thus, this observation may be biased by over-representation.

Our findings also identified doctors to have higher psychosocial impact from the pandemic. This is in contrary to the previous COVID-19 study in HCWs demonstrating that nurses had significantly higher levels of psychological distress compared to other HCWs.[7,21] There were several plausible explanations. Firstly, women made up more than half (54.5%) of the 220 doctors who responded to the survey. Secondly, 74.5% of doctors who participated in the study were young adults (21–30-year age group). Majority of them were house officers or medical officers who were engaged as frontline workers providing direct care to COVID-19 patients. In addition, they were from the pool of contract HCWs who must work without job security or appreciation. As the pandemic continued, some of these doctors had been deployed to cope with staff shortage in certain high-risk units, and this created a high level of stress and anxiety as they were not adequately trained and prepared for such working circumstances. Thirdly, there was constant fear of contracting the virus; fear of infecting families, friends, and colleagues and fear of social isolation and stigmatisation when diagnosed with COVID-19. The ensuing allostatic overload occurs when the environmental challenges exceed individual abilities to cope, resulting in psychosocial impact and poor health outcomes.[22] In addition, social media has been the platform where young adults interact and access information. The selective media coverage and overwhelming flow of negative information may perpetuate the sense of danger and uncertainly among them, resulting in a toll on their mental health.[23]

The findings from this study showed significant association between the self-rated health status, confidence level towards PPE in disease prevention, degree of familiarity in using PPE, adequacy of knowledge regarding the care of COVID-19 patients, and capability in answering questions asked by the public regarding the disease with the degree of psychosocial impact. Fear of self-infection and of infecting family has been one of the main risk factors associated with stress and adverse mental health outcomes.[7,9,21] The findings highlight the importance of infection control measures in reducing stress and anxiety among HCWs when vaccine and antiviral therapy were yet to be available for treatment. Numerous studies suggest the importance of PPE education and training to improve familiarity in usage and accurate timely update of COVID-19 information to HCWs, which were protective factors for mental outcomes during this pandemic.[7,9,21]

Perception towards sufficiency of PPE in workplace was not significantly associated with the psychosocial impact in this study. PPE is any type of equipment or clothing worn by HCWs to protect them against transmission of the COVID-19 virus. The shortage of PPE poses a challenge in containment of any infectious disease and causes undue stress and anxiety among HCWs due to perceived risk of infection.[7,9,21] Possible explanations for this finding were that at the time of this study, the COVID-19 pandemic in Malaysia was not as severe as in the rest of the world, and there had been daily briefing conducted by the Ministry of Health of Malaysia through social media platforms to provide real time updates, with HCWs often commended for the work and sacrifices that they had made.

The overall level of HCW satisfaction concerning organisational commitment and efforts to the COVID-19 pandemic was high, with a minimum score of 7 and above. There were several potential factors influencing the HCWs' sentiments during the pandemic. During the study period, Malaysia was at the flattened part of the epidemic curve, with low number of confirmed cases and death per million population. This has resulted in high expectation that the government policies in containment of pandemic were effective and the nation was progressing towards the return to normalcy. It is no surprise that the relevant stakeholders involved in the combat of pandemic, received uniformly high respondent ratings as HCWs understand the importance of multi-sector collaboration, at the local, national, and international level.

Our study does have limitations. Firstly, there may be a response bias due to the possibility that some non-respondents were either too stressed or not stressed at all to respond and, therefore, did not participate in this survey. Secondly, the study was conducted over 13 days and there was no longitudinal follow-up. Thirdly, the study was performed during the midst of the pandemic, where the survey may have missed the worst psychological distress among HCWs during the initial stages of the pandemic. Fourthly, self-reported responses may not correlate well with assessment by psychologist or psychiatrist. Finally, this study was of cross-sectional design with a convenience sample from a single tertiary care hospital in Malaysia, where the findings may not be representative of other hospitals or related clinical settings.

CONCLUSION

This study identified that doctors and female healthcare personnel have the highest risk of experiencing psychological distress during the COVID-19 pandemic. The risk factors associated with psychosocial impact among HCWs include self-rated health status, confidence level towards PPE in disease prevention, degree of familiarity in using PPE, adequacy of knowledge regarding care for COVID-19 patients, and capacity in answering questions asked by public regarding the disease. Strategies targeting the risk factors and early psychological support and intervention should be made available and accessible for all HCWs.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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ETHICAL APPROVAL

Ethical approval for the project was obtained from Medical Research and Ethics Committee (MREC), Ministry of Health of Malaysia, prior to commencement of the study (NMRR-20-1271-55333).

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Dropping the non-core subjects from undergraduate final professional examination: How it would impact the results

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ABSTRACT

Introduction: Observing the dearth of distinctions in the two decades of final professional medical examinations (FPE) caused concern. Multiple True False (MTF) tests with penalty scoring pulling down the scores was considered one reason. Another possible reason was having too many subjects covered in the MTF and Best Answer Question (BAQ) papers. This study aimed to explore the impact of dropping the non-core subjects with minimal inputs from MTF and BAQ papers and the students' views in this regard.

Materials and Methods: We examined the students' performance in the core and non-core subjects in MTF and BAQ papers and the impact of dropping the non-core subjects' contribution to the students' scores of the recent four final professional examinations. We also surveyed the opinions of the students, who took the FPE in the year 2000.

Results: The failure rates were significantly higher in non-core than core subjects ($p < 0.001$) except in one MTF paper. The mean scores were significantly lower in non-core than core subjects in all the four FPEs ($p < 0.05$) except in one MTF paper. Dropping the non-core subject items from MTF and BAQ showed an improvement in the scores of MTF, theory total, and most grand totals resulting in two more students reaching distinction status. A mere 3.8% of the students could thoroughly revise the non-core subjects before the FPE. Two-fifth of them believed that non-core subjects had a significant impact on theory performance. Only 31.5% favoured dropping the non-core subjects, and an equal number preferred a status quo, while the rest suggested a reduction in their weightage.

Conclusion: Most of the students considered the non-core subjects important in their career. However, very few of them could revise these subjects for the professional examination. The study demonstrated that dropping the non-core subjects from MTF and BAQ improved the students' final scores and helped more students to attain distinction status.

KEYWORDS:
Medical graduation criteria, Medical subjects tested, Core subjects, Non-core subjects, Distinction in Medicine,

INTRODUCTION

The goal of medical education is to produce capable medical professionals.[1] Students must undergo valid assessments in the final professional examination.[2,3] Such assessments should include evaluation of knowledge, its application, and clinical competence.[4] Our medical faculty at Universiti Malaysia Sarawak conducts a Final Professional Examination (FPE) and a Supplementary Final Professional Examination every year.[5] These examinations determine the medical students' eligibility to graduate, their grades, and their distinction status. The criteria for passing the FPE include 50% scores in each theory total, patient-based clinical, clinical total, and grand total. The faculty's FPE theory papers include MTF (15%), BAQ (15%), and MEQ (20%), besides the clinical components of OSCE, short cases, and a long case. The grand total (GT) comprises theory and clinical in a 50–50 proportion. The subjects included in the FPE theory papers of MTF and BAQ can be categorised as core subjects and non-core subjects. The number of questions of MTF and BAQ of each subject are given in brackets. The core subjects are Medicine (10-11), Surgery (10-8), Obstetrics and Gynaecology (8-8), Paediatrics (8-7), Orthopaedics (4-2), and Psychological Medicine (4-2); and the non-core subjects are Geriatrics (1), Dermatology (1), Anaesthesiology (1-1), Emergency Medicine (1-1), Radiology (1-1), Community Medicine & Public Health (3-2), Family Medicine (3-2), ENT (1-1), Ophthalmology (1-1), Clinical Diagnostic Laboratory (1-1), Forensic Medicine (1), and Ethics (1-2) in both the papers with minimal variations from year to year. All these subjects were taught and examined in the clinical years of year-3, year-4, and year-5, and obtaining reasonable scores in them was required for the eligibility to take the FPE. The candidates become eligible for distinction if they scored 75% of the grand total.

During this study period of four years (2017–2020), only two students out of the 458, who took the FPE, scored 75% marks. Several students, who deserved distinction based on their performance in the blocks and postings examinations during the five-year course, were deprived of it, as they fell short by a few marks. This raised questions about the assessment model followed by the faculty. It was noticed that the MTF with penalty scoring was consistently pulling down the scores in almost all examinations since the inception of the faculty, and the FPEs were no exception. Another likely reason was the overwhelming number of subjects covered in the MTF and

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BAQ papers, which carry 30% out of the 50% theory component. Fifty percent mark in the theory total is one criterion to pass the FPE, also 50% mark in the clinical total. It was considered that dropping the non-core subjects from the FPE's MTF and BAQ papers, while retaining them in the MEQ paper, would make a significant upgrade in the theory total and the final scores of the graduates.

In the instance of havinge more subjects, there was less coverage of topics in the theory papers. An all-inclusive final examination with minimal coverage of many topics within all subjects will not be a reliable and valid assessment.[6] The intention behind covering all the clinical subjects in the FPE was to make the exit examination comprehensive and horizontally integrated. However, including questions from the sub-specialities in negligible numbers would not achieve the desired goal. On the contrary, the need to revise the above-mentioned 18 subjects in a limited period of time overburdened the students. Would it not be better to cover the core subjects more broadly and leave out the non-core subjects already tested in the clinical postings? This study explored the impact of dropping the non-core subjects from the MTF and BAQ papers of the recent four FPEs and the students' views in this regard.

MATERIALS AND METHODS

Settings, Participants, and Sample Size

This cross-sectional study was conducted in the Faculty of Medicine and Health Sciences, Universiti Malaysia, Sarawak. The study consisted of two parts. Part one analysed the results of four FPEs of the years 2017 to 2020. The scores in MTF and BAQ were sorted to evaluate the students' performance in core subjects versus non-core subjects, and how dropping the non-core subjects would affect the theory total (TT) and GT scores. Part two was an online survey of the students, who participated at the FPE in the year 2020. We sought the students' opinions about the subjects covered in the FPE, and how much effort they could put into each subject during revision. Out of the 106 students, 104 participated in the survey with a response rate of 98.1%.

Data Collection Instruments and Data Collection Procedure

The FPEs' official results, question papers, and MTF optical mark reader (OMR) sheets were obtained from the academic office with administrative approval. For sorting the core and non-core item scores of MTF and BAQ tests, each student's OMR sheets of all the four FPEs were used. The faculty practised a penalty scoring system of minus one mark for every incorrect answer in MTF, which was not carried from one question to the next. We developed a questionnaire to assess the students' perceptions and opinions about the core and non-core subjects covered in the FPEs. It consisted of 18 questions about how important they considered each subject while preparing for the FPE. Specifically, 14 questions were about their preparation of six core subjects and eight non-core subjects and two questions on their opinions about how the inclusion of non-core subjects would have affected their final scores. One question was about their views on dropping the non-core subjects from FPE papers.

Data Analysis

Each student's MTF and BAQ scores were divided into those of core subjects and non-core subjects in the four FPEs. Students obtaining scores below 50% were counted as failed. The percentage mean scores with SD in all the categories, as below 50%, 70≤75% and 75% and above, total theory, and the grand total were calculated. Two-proportion z-test was done to determine the statistical difference in the pass and fail in core and non-core subjects. Independent t-test was done to compare the difference in mean scores in all the categories. A *p*-value less than 0.05 was considered statistically significant. The second part of the analysis was on students' views on the subjects covered in the FPE. The data from Microsoft Excel was imported to the IBM SPSS platform.[7] Descriptive analysis was done for the students' subject-wise preparation for FPE. On the Likert scale, '1' represented nil and '4' a thorough preparation. We analysed the subject-wise mean scores for FPE; the composite mean scores were calculated for core and non-core subjects. An independent t-test was done to determine the mean difference in preparation for core and non-core subjects. The students' opinions are presented in a frequency table. The student's opinions on keeping or dropping the non-core subjects in the FPE were analysed manually. We categorised the students' opinions about keeping or dropping the non-core subjects into four: 'no change', 'drop', 'reduce', and 'neutral'. The results are presented in six tables.

RESULTS

Table I demonstrated that the failure rates in MTF and BAQ were remarkably higher in the non-core division than in the core division in all the four FPEs ($p < 0.001$) except in the MTF paper of the year 2019 ($p > 0.05$), which was statistically insignificant.

Table II demonstrated that the MTF mean scores were significantly lower in the non-core division than in the core division in all the four FPEs ($p < 0.05$) except in the year 2019, in which the score was slightly higher in the non-core division, which was not statistically significant ($p > 0.05$). In BAQ, the mean scores were significantly lower in the non-core division than in the core division in all four years, although the difference was not significant in 2018 ($p > 0.05$).

Table III demonstrated that in all the non-core included vs non-core dropped comparisons, NCD mean scores were higher, except in the MTF of 2019, which was not significant. Theory totals and grand totals also showed higher values in the NCD, although not significant except in the TT of 2017. Theory total and grand total showed an improvement in the scoring trend and a decrease in the failure rates on dropping the non-core division. Theory failures decreased by 9, and high scorers increased by 17 in NCD. In GT number of failures decreased by four, and number of distinctions increased by two. One candidate moved from high scorer to distinction in 2018, which explains the drop from 6 to 5 in the GT of 2018.

Table I: Failure rates (percentage) in core and non-core divisions of MTF and BAQ

Year	St. N	MTF		*p*-value	BAQ		*p*-value
		Core Fail %	Non-core Fail %		Core Fail %	Non- core Fail %	
2017	112	66.96	100	$p < 0.001$	27.68	62.5	$p < 0.001$
2018	118	61.02	94.07	$p < 0.001$	0	10.17	$p < 0.001$
2019	122	79.51	68.85	$p > 0.05$	0	24.59	$p < 0.001$
2020	106	83.96	99.06	$p < 0.001$	4.72	26.42	$p < 0.001$

Notes. *p*-value reached from two-proportion z-test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. St. N = number of students; MTF = multiple true false; BAQ = best answer questions; Core = core division; Non-core = non-core division. Fifty percent was the pass score.

Table II: Mean scores (percentage) in core and non-core divisions of MTF and BAQ

Year	N	MTF		*p*-value	BAQ		*p*-value
		Core Mean (SD)	Non-core Mean (SD)		Core Mean (SD)	Non-core Mean (SD)	
2017	112	46.17(8.6)	29.74(6.8)	$p < 0.001$	55.57(9.6)	42.63(11.3)	$p < 0.001$
2018	118	48.39(8.0)	39.05(6.8)	$p < 0.001$	63.49 (9.5)	61.08 (12.7)	$p > 0.05$
2019	122	44.36(7.1)	45.14(7.6)	$p > 0.05$	73.00 (8.5)	56.79 (13.0)	$p < 0.001$
2020	106	45.96(8.9)	31.79(7.7)	$p < 0.001$	60.58(8.0)	57.84 (11.8)	$p < 0.05$

Notes. p-value reached from independent t-test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
N = number of students; MTF = multiple true false; BAQ = best answer questions; SD = standard deviation.

Table III: The impact of dropping the non-core subjects in the four FPEs: mean scores, failures, and high scorers

Year (N)	MTF	BAQ	TT				GT			
			NCI vs. NCD				NCI vs. NCD			
	NCI vs. NCD	NCI vs. NCD	Mean	<50	70-75	≥75	Mean	<50	70-75	≥75
2017 (112)	41.79 - 46.17***	52.46 - 55.57**	55.1 – 57.31*	19 – 12	2 - 6	0 - 0	56.90 – 58.00	9 – 6	1 - 4	0 - 0
2018 (118)	45.79 - 48.39**	62.81 - 63.49	58.56 - 59.55*	8 – 6	4 - 7	0 - 2	59.18 – 59.67	2 – 2	6 - 5	0 - 1
2019 (122)	44.7 - 44.36	68.46 - 73.00***	60.84 – 62.1	0 – 0	8 - 9	0 - 4	60.64 – 61.27	0 – 0	6 - 8	0 - 1
2020 (122)	42.28 - 45.96**	59.87 – 60.58	57.67 – 5 8.99	5 – 5	4 - 6	0 - 1	59.05 – 59.71	4 – 3	4 - 7	2 - 2

Notes. *p*-value reached from independent t-test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. N = student numbers; MTF = multiple true false; BAQ = best answer questions; TT = theory total; GT = grand total; NCI = non-core included (as it is currently practised); NCD = non-core dropped (as explored in this study).

Table IV: Students' subject-wise preparation for the examination of 2020

	Subjects	Mean	SD	Mean(SD)
Core subjects	Surgery	3.24	0.63	3.06(0.49)
	Obstetrics and Gynaecology	3.19	0.62	
	Paediatrics	3.21	0.57	
	Internal Medicine	3.17	0.58	
	Orthopaedics	2.87	0.70	
	Psychological Medicine	2.69	0.70	
Non-core subjects	Emergency Medicine	2.94	0.80	2.34(0.65)
	Radiology	2.50	0.82	
	Family Medicine	2.39	0.82	
	CMPH	2.29	0.80	
	ENT	2.22	0.72	
	Ophthalmology	2.14	0.76	
	CDL	2.12	0.82	
	Anaesthesiology	2.11	0.87	

Table V: Students' opinions about the inclusion of non-core subjects in the final professional examinations

Opinions	N	%
About time spent on non-core subjects		
I did a thorough revision of all of them	4	3.8
I did revise some of them partly	75	72.1
I had no time to look them up	22	21.2
Not bothered much	3	2.9
About the perceived impact of non-core subjects on theory performance		
Little impact	8	7.7
Some impact	36	34.6
Significant impact	46	44.2
Substantial impact	14	13.5
To keep or drop non-core subjects		
Keep them as usual	42	40.4
Drop them from FPE	41	39.4
Reduce them	15	14.4
Neutral	6	5.8

The students, who favoured keeping the non-core subjects in FPE, wrote:

"….. For me, non-core subjects should not be removed as some of the diseases listed on the non-core subjects are common, and students should a least have some knowledge of the disease".

"…….I think a non-core subject should still be included as it is also a part of medical 'things' even though only a small part of it but still important".

"…….I do not agree if non-core subjects are removed from FPE as those subjects are also important in medicine, but the questions must be more focused on common cases".

"…..I do not think it should be removed. We were not prepared because we did not know what to expect from the questions since we were too focused on the core subjects. Maybe the important topics from the non-core can be highlighted for us to focus more on that. I think the coverage for the core subjects is fair enough, which is even more than the non-core subjects".

The students, who were in favour of dropping the non-core subjects, wrote:

"…….Non-core subjects can just be omitted since the marks weightage is also little. Students will have more time to revise thoroughly on the core subjects".

"……..Just remove them. Why bother testing on those when core subjects are much more important clinically".

"…….I think core subjects are important in theory examination. Non-core subjects already covered during the end of posting examination should be good enough".

The students, who gave mixed opinions on non-core subjects, wrote:

"……It is better to include non-core subjects as well, as it is what commonly seen in our community. Personally, I am afraid that I might miss a patient's particular condition; for example, in ENT posting, the patient presented with epistaxis, NPC must come first in my mind".

"…….It is essential to include non-core subjects. We need that knowledge when we start working later on. Of course, core subjects are the highlight, but non-core subjects should not be forgotten".

"…….The non-core subject should not be removed, but questions can be asked to correlate with the core subjects. For example, thyroid eye disease or diabetic retinopathy in ophthalmology (related to an endocrine problem in medicine), nasal polyp in ENT (related to bronchial asthma in medicine), food poisoning in the public health aspect, etc. rather than having those unrelated things like researches in public health".

DISCUSSION

Directly pertaining to our study findings

At the outset, we must admit that this study stands alone with no other studies of its kind to compare with. Our attempts to gather information regarding the subject coverage in FPE of other universities also did not bear fruit. However, we could reach important conclusions from the data of our faculty's four FPE results. Our study focused on the students' performance in the core and non-core divisions of theory assessments in four recent FPEs and explored the impact of dropping the non-core division from MTF and BAQ on the failure rates (<50% scores), theory total, and grand total scores. In all the MTF data, penalty scoring was used, as in the official results. The apparent reason for the significant differences between NCI and NCD scores was the students' better performance in the core subjects. The results showed significantly higher failure rates and significantly lower mean scores in the non-core division compared to the core division in MTF and BAQ tests of the four examinations with one insignificant exception in the MTF of 2019 (Tables I and II). It was also illustrated that in all the NCI-NCD comparisons, NCD mean scores were higher except in the MTF of 2019 (Table III). The absence of a statistically significant increase in the theory totals, except in 2017, and grand totals could be explained as the total contribution of MTF and BAQ were only 30%. The theory total includes MEQ with 20% and the grand total includes clinical components of 50%. An increase in the number of students scoring 75% or above in the GT (distinction) with NCD was seen in 2018 and 2019, while the theory total improved in 2018, 2019, and 2020. Improvement in scores and decrease in failure rates were seen in all the years with NCD (Table III). These findings support our conclusion that dropping the non-core subjects from MTF and BAQ in the FPE would improve the overall student performance and help more students to attain deserving higher scores and distinction status in the FPEs.

Students' preparation for the final professional examination of 2020, and their views

Table IV illustrated the subject-wise preparation for the FPEs on a Likert scale. Among core subjects, the highest score was for Surgery (Mean = 3.24, SD = 0.63) followed by Obstetrics and Gynaecology (Mean = 3.19, SD = 0.62), and the lowest score was for Psychological Medicine (Mean = 2.69, SD = 0.70). In contrast, in non-core subjects, the highest score was for Emergency Medicine (Mean = 2.94, SD = 0.82) followed by Radiology (Mean = 2.50, SD = 0.82), and the lowest for Anaesthesiology (Mean = 2.11, SD = 0.87). The difference between the overall mean scores of core subjects (Mean = 3.06, SD = 0.49) and non-core subjects (Mean = 2.34, SD = 0.65) was statistically significant ($p < 0.001$) indicating that the students devoted more time and attached more importance to the core subjects. Students devoted more time to revising core subjects than non-core subjects, as they might have correctly estimated the latter's lower impact on the final scores. Although they could not find enough time to revise them sufficiently, they did not underestimate the importance of non-core subjects in their career. Their freely expressed opinions supported these findings. Most of the students favoured dropping the non-core subjects altogether or reducing their content in the FPE (Table V).

Why this issue regarding student preparedness for FPE deserves attention

The intention of including all important subjects in the FPE for making it a comprehensive assessment was understandable. However, how it affected students' preparations and performance in the FPE appeared to be overlooked. The current trend is towards relying more on continuous assessment than a single all-inclusive final examination.[6,8] It is worth noting that our medical faculty has a well-structured continuous assessment throughout the course. We suggest modifying the FPE by dropping the non-core subjects and replacing them with more questions from the core subjects in MTF and BAQ papers would be beneficial. This change would enable students to focus more and revise the core subjects better helping them to secure higher scores. It would also improve the reliability and validity of these tests as broader coverage of the core subjects will be possible.[9,10] Our results showed that such an amendment in the FPE would reward the deserving candidates with distinctions, too. Officially dropping the non-core subjects from MTF and BAQ does not mean that these subjects would not be tested at all in the FPE. The MEQ papers include parts of non-core subjects, while many MTF and BAQ items also would contain parts of non-core subjects in line with the faculty's philosophy of vertical and horizontal integration in the curriculum.

LIMITATIONS OF THE STUDY

This was a novel single-institution study with no possible comparisons to be made as there were no similar studies having been published prior to this study. Our attempts to gather more information about the practices in other medical schools were not successful enough to be presented here. Nor could we find publications dealing with the issue of the number of subjects covered in the final medical degree professional examinations.

CONCLUSION

This study establishes that including the non-core subjects in the final professional theory examination overburdens the students, impedes adequate revision of the subjects, and lowers their scores in the final professional examination. Most students consider the knowledge of non-core subjects equally important as that of the core subjects for their future career as doctors. However, more students favour dropping the non-core subjects altogether or reducing their weight in the MTF and BAQ papers. Our study concludes that dropping the non-core subjects and augmenting the coverage of core subjects in the final professional examination's MTF and BAQ papers would help to improve the students' preparations and their theory total and grand total scores, and moreover would help the deserving students to graduate with distinction.

ETHICAL APPROVAL

The Institutional Review Board approved this study (Ref # FME/21/72 Dated: 26 April 2021). We obtained informed consent, maintained data confidentiality and anonymity of the survey participants.

CONFLICT OF INTEREST

All authors have declared no competing interests.

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ORIGINAL ARTICLE

In vitro activity of ceftazidime-avibactam against clinical isolates of Enterobacterales and *Pseudomonas aeruginosa* collected in Malaysia: Results from the ATLAS Programme, 2013 to 2019

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ABSTRACT

Introduction: There has been a steady rise in antimicrobial resistance among common pathogens in Malaysia. This study aims to determine the *in vitro* antimicrobial activities of ceftazidime-avibactam and its comparators against clinical isolates of Enterobacterales and *Pseudomonas aeruginosa* collected in Malaysia from 2013 to 2019, and to determine the rates of resistance among these isolates.

Materials and Methods: In this retrospective study, four participating study centres located in East (N = 1) and West (N = 3) Malaysia contributed to the collection of clinical isolates of Enterobacterales and *P. aeruginosa* from 2013 to 2019. Antimicrobial minimum inhibitory concentrations (MICs) and percentage susceptibilities were interpreted according to Clinical Laboratory Standards Institute (CLSI) breakpoints, except for tigecycline and colistin, which utilised the United States Food and Drug Administration (US FDA) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, respectively.

Results: A total of 1,073 isolates of Enterobacterales and 332 isolates of *P. aeruginosa* were collected in Malaysia from the four centres. Among Enterobacterales isolates, the highest percentages of susceptibility were seen with ceftazidime-avibactam (99.2%), meropenem (98.9%), and tigecycline (96.9%). Whereas *P. aeruginosa* isolates demonstrated the highest susceptibilities to colistin (95.6%), followed by ceftazidime-avibactam (93.1%) and cefepime (87.1%). All metallo-β-lactamase (MBL)-negative isolates of Enterobacterales, including ceftazidime-nonsusceptible, meropenem-nonsusceptible, and colistin-resistant phenotypes, were susceptible to ceftazidime-avibactam. Furthermore, ceftazidime-avibactam demonstrated the highest percentage of susceptibility (97.1%) against multidrug-resistant (MDR) isolates of Enterobacterales.

Conclusion: Ceftazidime-avibactam exhibited potent *in vitro* activity against clinical isolates of Enterobacterales and *P. aeruginosa* collected in Malaysia from 2013 to 2019. The results of this study show that ceftazidime-avibactam should be considered in the treatment of indicated infections caused by susceptible strains of aerobic Gram-negative pathogens and is a valuable alternative to carbapenems.

KEYWORDS:
ATLAS, carbapenem-resistant, ceftazidime-avibactam, colistin-resistant, Enterobacterales, Gram-negative, Malaysia, Pseudomonas aeruginosa, surveillance

INTRODUCTION

Rising antimicrobial resistance has led to increased morbidity and mortality rates associated with infectious diseases and is now an alarming global issue. The rising resistance rates, including the emergence of multidrug-resistant (MDR) organisms, can be attributed to the excessive and suboptimal use of antibiotics in clinical practice.[1,2] Similarly in Malaysia, a steady rise in antimicrobial resistance among common pathogens has been observed.[2] Of note, the World Health Organisation (WHO) has classified both carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* as critical priority pathogens for research and development, whereas the Centers for Disease Control and Prevention (CDC) has classified CRE as an urgent threat that requires aggressive action.[3,4] CREs produce carbapenemases, enzymes that hydrolyse the β-lactam antibiotics (e.g. carbapenems, cephalosporins, penicillins, and aztreonam) and are resistant against most β-lactamase inhibitors.[5] Common carbapenemases include class A *Klebsiella pneumoniae* carbapenemases (KPCs), class B metallo-β-lactamases (MBLs) including imipenemase (IMP), New Delhi MBL (NDM), and Verona Integron-encoded MBL (VIM) types, and class D Oxacillinase (OXA) β-lactamases.[1]

Ceftazidime-avibactam is a combination of the third-generation cephalosporin, ceftazidime, and the novel, non-β-lactam β-lactamase inhibitor, avibactam. Avibactam has potent *in vitro* activity against a broad range of β-lactamases, including Ambler class A (extended-spectrum β-lactamases, KPCs), class C (AmpC), and some class D (OXA-48) enzymes. Therefore, combination with avibactam extends ceftazidime's spectrum of activity to cover MDR

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Enterobacterales and *P. aeruginosa* strains; however, an important limitation of the combination is its inability to inhibit MBL-producing isolates (i.e. NDM, VIM, IMP).[6,7]

Ceftazidime-avibactam is approved for the treatment of adults with complicated intra-abdominal infections (in combination with metronidazole), complicated urinary tract infections (including pyelonephritis), and hospital-acquired pneumonia (including ventilator-associated pneumonia). In Europe, ceftazidime-avibactam is also approved for the treatment of adult patients with other infections caused by aerobic Gram-negative organisms with limited treatment options.[7,8] Currently, there is a lack of studies that specifically describe the *in vitro* activity of ceftazidime-avibactam against clinical isolates of Enterobacterales and *P. aeruginosa* in Malaysia. This study aims to determine the *in vitro* antimicrobial activities of ceftazidime-avibactam and its comparators against clinical isolates of Enterobacterales and *P. aeruginosa* collected in Malaysia from 2013 to 2019, and to determine the rates of resistance among these isolates, using the data from the Antimicrobial Testing Leadership and Surveillance (ATLAS) programme.

MATERIALS AND METHODS

In this retrospective study, four participating study centres located in East (N = 1) and West (N = 3) Malaysia contributed to the collection of clinical isolates of Enterobacterales (i.e., *Citrobacter* spp., *Enterobacter* spp., *Escherichia* spp., *Serratia* spp., *Klebsiella* spp., and *Proteus* spp.) and *P. aeruginosa* from 2013 to 2019. Relevant clinical isolates were obtained from hospitalised patients with complicated intra-abdominal infections, complicated urinary tract infections, complicated skin and skin structure infections, lower respiratory tract infections, and bloodstream infections.[9] The isolates were then identified by each participating study centre and stored in tryptic soy broth (supplied by the International Health Management Associates [IHMA]) with glycerol at –70°C, and shipped to a central laboratory (IHMA Inc., Schaumburg, IL, USA) for susceptibility testing.[9] Only isolates identified as a potential causative agent of a patient's infection were included in these studies.[9] Isolate identification was confirmed by IHMA using matrix-assisted laser desorption ionisation–time of flight mass spectrometry (MALDI Biotyper; Bruker Daltonics, Billerica, MA, USA).

Antimicrobial susceptibility testing was performed following the Clinical and Laboratory Standards Institute (CLSI) standard method and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines of the European Society of Clinical Microbiology and Infectious Diseases, using custom 96-well broth microdilution panels prepared in-house at IHMA or by Trek (Thermo Fisher Scientific, Oakwood Village, OH, USA).[10] The minimum inhibitory concentrations (MICs) were interpreted using current CLSI breakpoints[11] with the following exceptions: Tigecycline and colistin MICs were interpreted using the United States Food and Drug Administration (US FDA)[12] and EUCAST[13] breakpoints, respectively. Polymerase chain reaction and Sanger sequencing or whole-genome sequencing were used to screen isolates of Enterobacterales and *P. aeruginosa* for the presence of known resistant mechanisms, such as the presence or alteration in genes encoding β-lactamases and penicillin-binding proteins.

Data considered evaluable by IHMA were collated by a data management team and incorporated by Micron Research (Micron, Ely, UK) into the ATLAS database, an interactive platform available at www.atlas-surveillance.com.[14] In this study, the data were analysed for ceftazidime-avibactam, and the following comparator agents: imipenem, meropenem, cefepime, ceftazidime, tigecycline, colistin, and piperacillin-tazobactam. The data for this study were extracted in June 2021; however, the ATLAS database is continuously updated, with new resources being added regularly (i.e. every 6–8 months).[14] Ethical clearance was obtained from the National Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. This study was registered under the National Medical Research Registry (NMRR-18-1271-39749).

RESULTS

Over the 7-year period, 1,405 isolates (1,073 isolates of Enterobacterales; 332 isolates of *P. aeruginosa*) were collected from participating hospitals, including Hospital Kuala Lumpur, Hospital Sultanah Aminah, Hospital Sungai Buloh, and Sarawak General Hospital. Of the 1,073 isolates of Enterobacterales tested, 99.2% were susceptible to ceftazidime-avibactam (MIC_{90}, 0.25 mg/L), with lower percentages of susceptibility observed with meropenem (98.9%), tigecycline (96.9%), imipenem (91.1%), piperacillin-tazobactam (89.5%), colistin (85.9%), ceftazidime alone (75.9%), and cefepime (75.3%). Ceftazidime-avibactam MIC_{90} values for each species or species group within the Enterobacterales order ranged from 0.06 mg/L (*Proteus* spp.) to 0.5 mg/L (*Enterobacter* spp., *K. pneumoniae* and *Serratia* spp.), whereas percentages of susceptibility to ceftazidime-avibactam were 98.1%, 98.4%, and 100% among *Enterobacter* spp., *K. pneumoniae*, and among other species or species groups of Enterobacterales isolates (*E. coli, K. aerogenes, K. oxytoca, K. variicola, Citrobacter* spp., *Proteus* spp., and *Serratia* spp.), respectively. Isolates of *Proteus* and *Serratia* demonstrate nonsusceptibility to colistin as they are naturally resistant to polymyxins.[15] Among isolates of Enterobacterales, only eight MBL-positive isolates were found within groups of *K. pneumoniae* (6/400 isolates,1.5%) and *Enterobacter* spp. (2/122 isolates,1.6%). Hence, percentages of susceptibility to ceftazidime-avibactam were 1.6% and 1.9% higher for MBL-negative isolates of *K. pneumoniae* and *Enterobacter* spp., respectively, compared with data sets that included all isolates. All Enterobacterales isolates that were MBL-negative exhibited 100% susceptibility to ceftazidime-avibactam. The susceptibility of Enterobacterales isolates to imipenem (91.1%) was lower compared with meropenem (98.9%) owing to the presence of 73 isolates of *Proteus* spp. (6.8% of all Enterobacterales isolates); the genus *Proteus* has innately higher imipenem MICs compared with meropenem.[11] Among the 332 isolates of *P. aeruginosa*, 95.6% (MIC_{90}, 2 mg/L), 93.1% (MIC_{90}, 8 mg/L), 87.1%, 83.4%, 83.4%, 81.6%, and 78.6% were susceptible to colistin, ceftazidime-avibactam, cefepime, ceftazidime alone, meropenem, piperacillin-tazobactam, and imipenem, respectively. When only MBL-negative isolates of *P. aeruginosa* were considered, the percentage of susceptibility to ceftazidime-avibactam was the highest (97.9%) compared with the other agents (Table I).

Table I: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	MIC (mg/L)				
		N	50%	90%	Range	% susceptible[b]
Enterobacterales	Ceftazidime-avibactam	956	0.12	0.25	≥0.015 to ≤256	99.2
	Ceftazidime	1,073	0.25	64	≥0.03 to ≤256	75.9
	Cefepime	1,073	0.12	32	≥0.12 to ≤64	75.3
	Piperacillin-tazobactam	1,073	2	32	≥0.12 to ≤256	89.5
	Imipenem	956	0.25	1	≥0.06 to ≤16	91.1
	Meropenem	1,073	0.06	0.12	≥0.015 to ≤32	98.9
	Colistin	703	0.5	8	≥0.12 to ≤16	85.9
	Tigecycline	1,073	0.5	2	≥0.06 to ≤16	96.9
Enterobacterales, MBL-negative	Ceftazidime-avibactam	948	0.12	0.25	≥0.015 to ≤4	100
	Ceftazidime	1,065	0.25	32	≥0.03 to ≤256	76.4
	Cefepime	1,065	0.12	32	≥0.12 to ≤64	75.9
	Piperacillin-tazobactam	1,065	2	16	≥0.12 to ≤256	90.1
	Imipenem	948	0.25	1	≥0.06 to ≤8	91.9
	Meropenem	1,065	0.06	0.06	≥0.015 to ≤4	99.6
	Colistin	695	0.5	8	≥0.12 to ≤16	85.8
	Tigecycline	1,065	0.5	2	≥0.06 to ≤16	96.9
Klebsiella pneumoniae	Ceftazidime-avibactam	365	0.12	0.5	≥0.015 to ≤256	98.4
	Ceftazidime	400	0.5	128	≥0.03 to ≤256	63.0
	Cefepime	400	0.12	32	≥0.12 to ≤64	62.8
	Piperacillin-tazobactam	400	4	128	≥0.5 to ≤256	81.0
	Imipenem	365	0.25	0.5	≥0.06 to ≤16	97.3
	Meropenem	400	0.06	0.12	≥0.015 to ≤32	97.8
	Colistin	275	0.5	1	≥0.12 to ≤16	98.9
	Tigecycline	400	0.5	2	≥0.25 to ≤16	97.8
Klebsiella pneumoniae, MBL-negative	Ceftazidime-avibactam	359	0.12	0.5	≥0.015 to ≤4	100
	Ceftazidime	394	0.25	64	≥0.03 to ≤256	64.0
	Cefepime	394	0.12	32	≥0.12 to ≤64	63.7
	Piperacillin-tazobactam	394	4	128	≥0.5 to ≤256	82.2
	Imipenem	359	0.25	0.5	≥0.06 to ≤4	98.9
	Meropenem	394	0.12	0.12	≥0.015 to ≤4	99.2
	Colistin	269	0.5	1	≥0.12 to ≤16	98.9
	Tigecycline	394	0.5	2	≥0.25 to ≤16	97.7
Klebsiella spp. (other than *Klebsiella pneumoniae*)[c]	Ceftazidime-avibactam	20	0.12	0.25	≥0.06 to ≤0.25	100
	Ceftazidime	26	0.25	2	≥0.06 to ≤32	92.3
	Cefepime	26	0.12	0.5	≥0.12 to ≤0.5	100
	Piperacillin-tazobactam	26	4	4	≥0.5 to ≤32	92.3
	Imipenem	20	0.5	2	≥0.12 to ≤2	90.0
	Meropenem	26	0.06	0.12	≥0.03 to ≤0.12	100
	Colistin	18	0.25	0.5	≥0.12 to ≤2	100
	Tigecycline	26	0.5	0.5	≥0.06 to ≤1	100
Enterobacter spp.[d]	Ceftazidime-avibactam	105	0.25	0.5	≥0.03 to ≤256	98.1
	Ceftazidime	122	0.5	64	≥0.06 to ≤256	80.3
	Cefepime	122	0.12	8	≥0.12 to ≤64	83.6
	Piperacillin-tazobactam	122	2	16	≥0.5 to ≤256	91.8
	Imipenem	105	0.5	2	≥0.06 to ≤16	87.6
	Meropenem	122	0.06	0.12	≥0.015 to ≤32	98.4
	Colistin	76	0.5	16	≥0.12 to ≤16	85.5
	Tigecycline	122	0.5	1	≥0.12 to ≤2	100
Enterobacter spp., MBL-negative	Ceftazidime-avibactam	103	0.25	0.5	≥0.03 to ≤2	100
	Ceftazidime	120	0.5	32	≥0.06 to ≤256	81.7
	Cefepime	120	0.12	8	≥0.12 to ≤64	85.0
	Piperacillin-tazobactam	120	2	16	≥0.5 to ≤256	93.3
	Imipenem	103	0.5	2	≥0.06 to ≤4	89.3
	Meropenem	120	0.12	0.12	≥0.015 to ≤0.5	100
	Colistin	74	0.5	16	≥0.12 to ≤16	85.1
	Tigecycline	120	0.5	1	≥0.12 to ≤2	100

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Table I: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	MIC (mg/L)				
		N	50%	90%	Range	% susceptible[b]
Escherichia coli	Ceftazidime-avibactam	321	0.06	0.25	≥0.015 to ≤4	100
	Ceftazidime	359	0.25	32	≥0.03 to ≤256	80.2
	Cefepime	359	0.12	32	≥0.12 to ≤64	77.7
	Piperacillin-tazobactam	359	2	8	≥0.12 to ≤256	95.5
	Imipenem	321	0.25	0.25	≥0.06 to ≤2	99.7
	Meropenem	359	0.03	0.06	≥0.015 to ≤1	100
	Colistin	229	0.5	1	≥0.12 to ≤4	96.5
	Tigecycline	359	0.25	0.5	≥0.06 to ≤8	99.2
Citrobacter spp.[e]	Ceftazidime-avibactam	40	0.12	0.25	≥0.03 to ≤2	100
	Ceftazidime	41	0.25	64	≥0.12 to ≤256	78.1
	Cefepime	41	0.12	32	≥0.12 to ≤64	82.9
	Piperacillin-tazobactam	41	4	128	≥1 to ≤256	85.4
	Imipenem	40	0.25	0.5	≥0.12 to ≤2	95.0
	Meropenem	41	0.06	0.06	≥0.015 to ≤2	97.6
	Colistin	28	0.25	1	≥0.12 to ≤1	100
	Tigecycline	41	0.25	0.5	≥0.12 to ≤1	100
Proteus spp.[f]	Ceftazidime-avibactam	73	0.06	0.06	≥0.03 to ≤0.12	100
	Ceftazidime	73	0.06	0.25	≥0.03 to ≤8	98.6
	Cefepime	73	0.12	2	≥0.12 to ≤32	91.8
	Piperacillin-tazobactam	73	0.25	1	≥0.25 to ≤128	98.6
	Imipenem	73	2	4	≥0.25 to ≤8	23.3
	Meropenem	73	0.06	0.12	≥0.06 to ≤1	100
	Colistin	51	16	16	≥8 to ≤16	0
	Tigecycline	73	2	4	≥0.25 to ≤8	75.3
Serratia spp.[g]	Ceftazidime-avibactam	32	0.25	0.5	≥0.06 to ≤0.5	100
	Ceftazidime	52	0.5	1	≥0.06 to ≤256	92.3
	Cefepime	52	0.12	0.5	≥0.12 to ≤64	94.2
	Piperacillin-tazobactam	52	2	8	≥0.25 to ≤128	96.2
	Imipenem	32	1	1	≥0.25 to ≤2	96.9
	Meropenem	52	0.06	0.12	≥0.03 to ≤0.25	100
	Colistin	26	16	16	≥4 to ≤16	0
	Tigecycline	52	1	2	≥0.25 to ≤4	94.2
Pseudomonas aeruginosa	Ceftazidime-avibactam	303	2	8	≥0.5 to ≤256	93.1
	Ceftazidime	332	2	32	≥0.5 to ≤256	83.4
	Cefepime	332	2	16	≥0.5 to ≤64	87.1
	Piperacillin-tazobactam	332	8	128	≥0.25 to ≤256	81.6
	Imipenem	303	2	16	≥0.25 to ≤16	78.6
	Meropenem	332	0.5	8	≥0.06 to ≤32	83.4
	Colistin	274	1	2	≥0.25 to ≤8	95.6
Pseudomonas aeruginosa, MBL-negative	Ceftazidime-avibactam	288	2	4	≥0.5 to ≤256	97.9
	Ceftazidime	317	2	16	≥0.5 to ≤256	79.8
	Cefepime	317	2	8	≥0.5 to ≤64	55.8
	Piperacillin-tazobactam	317	8	32	≥0.25 to ≤256	85.5
	Imipenem	288	2	16	≥0.25 to ≤16	25.0
	Meropenem	317	0.5	4	≥0.06 to ≤32	82.3
	Colistin	260	1	2	≥0.25 to ≤8	95.4

[a]Isolates of Enterobacterales (N = 1,073) and *Pseudomonas aeruginosa* (N = 332) were collected in Malaysia as part of the ATLAS program from 2013 to 2019.
[b]Percentage susceptibilities were interpreted according to CLSI breakpoints, except for tigecycline and colistin, which utilised US FDA and EUCAST breakpoints, respectively.
[c]*Klebsiella* spp. (other than *Klebsiella pneumoniae*) included *Klebsiella aerogenes* (N = 14), *Klebsiella oxytoca* (N = 6) and *Klebsiella variicola* (N = 6).
[d]The *Enterobacter* spp. included *Enterobacter aerogenes* (N = 20), *Enterobacter asburiae* (N = 8), *Enterobacter cloacae* (N = 84), *Enterobacter kobei* (N = 3), *Enterobacter xiangfangensis* (N = 5), and *Enterobacter*, non-speciated (N = 2).
[e]The *Citrobacter* spp. included *Citrobacter amalonaticus* (N = 1), *Citrobacter freundii* (N = 5), and *Citrobacter koseri* (N = 35).
[f]*Proteus* spp. included *Proteus hauseri* (N = 1), *Proteus mirabilis* (N = 57), and *Proteus vulgaris* (N = 15).
[g]*Serratia* spp. included *Serratia marcescens* (N = 51) and *Serratia rubidaea* (N = 1).

Table II: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against ceftazidime-nonsusceptible isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	N	MIC (mg/L)			% susceptible[b]
			50%	90%	Range	
Enterobacterales	Ceftazidime-avibactam	228	0.25	1	≥0.015 to ≤256	96.5
	Ceftazidime	259	32	256	≥8 to ≤256	0
	Cefepime	259	32	64	≥0.12 to ≤64	12.7
	Piperacillin-tazobactam	259	16	256	≥0.5 to ≤256	63.3
	Imipenem	228	0.25	1	≥0.12 to ≤16	92.5
	Meropenem	259	0.06	0.25	≥0.015 to ≤32	95.4
	Colistin	172	0.5	1	≥0.12 to ≤16	93.0
	Tigecycline	259	0.5	2	≥0.06 to ≤8	97.3
Enterobacterales, MBL-negative	Ceftazidime-avibactam	220	0.25	1	≥0.015 to ≤4	100
	Ceftazidime	251	32	256	≥8 to ≤256	0
	Cefepime	251	32	64	≥0.12 to ≤64	13.2
	Piperacillin-tazobactam	251	8	256	≥0.5 to ≤256	65.3
	Imipenem	220	0.25	1	≥0.12 to ≤4	95.9
	Meropenem	251	0.12	0.12	≥0.015 to ≤4	98.4
	Colistin	164	0.5	1	≥0.12 to ≤16	92.7
	Tigecycline	251	0.5	2	≥0.06 to ≤8	97.2
Klebsiella spp.	Ceftazidime-avibactam	138	0.25	1	≥0.03 to ≤256	95.7
	Ceftazidime	150	32	256	≥8 to ≤256	0
	Cefepime	150	32	64	≥0.12 to ≤64	4.7
	Piperacillin-tazobactam	150	16	256	≥0.5 to ≤256	52.7
	Imipenem	138	0.25	1	≥0.12 to ≤16	92.8
	Meropenem	150	0.06	0.25	≥0.015 to ≤32	94.0
	Colistin	96	0.5	1	≥0.12 to ≤4	97.9
	Tigecycline	150	1	2	≥0.25 to ≤8	96.7
Klebsiella spp., MBL-negative	Ceftazidime-avibactam	132	0.25	1	≥0.03 to ≤4	100
	Ceftazidime	144	32	256	≥8 to ≤256	0
	Cefepime	144	32	64	≥0.12 to ≤64	4.9
	Piperacillin-tazobactam	144	16	256	≥0.5 to ≤256	54.9
	Imipenem	132	0.25	1	≥0.12 to ≤4	97.0
	Meropenem	144	0.12	0.25	≥0.015 to ≤4	97.9
	Colistin	90	0.5	1	≥0.12 to ≤4	97.8
	Tigecycline	144	1	2	≥0.25 to ≤8	96.5
Enterobacter spp.	Ceftazidime-avibactam	18	0.5	256	≥0.12 to ≤256	88.9
	Ceftazidime	24	64	256	≥8 to ≤256	0
	Cefepime	24	8	64	≥0.25 to ≤64	41.7
	Piperacillin-tazobactam	24	16	128	≥1 to ≤256	58.3
	Imipenem	18	1	8	≥0.25 to ≤16	83.3
	Meropenem	24	0.12	0.5	≥0.03 to ≤32	91.7
	Colistin	17	0.5	8	≥0.25 to ≤16	82.4
	Tigecycline	24	0.5	2	≥0.25 to ≤2	100
Enterobacter spp., MBL-negative	Ceftazidime-avibactam	16	0.5	1	≥0.12 to ≤2	100
	Ceftazidime	22	64	128	≥8 to ≤256	0
	Cefepime	22	8	64	≥0.25 to ≤64	45.5
	Piperacillin-tazobactam	22	16	64	≥1 to ≤256	63.6
	Imipenem	16	0.5	1	≥0.25 to ≤2	93.8
	Meropenem	22	0.12	0.5	≥0.03 to ≤0.5	100
	Colistin	15	0.5	8	≥0.25 to ≤16	80.0
	Tigecycline	22	0.5	2	≥0.25 to ≤2	100
Escherichia coli	Ceftazidime-avibactam	61	0.12	0.25	≥0.015 to ≤4	100
	Ceftazidime	71	32	64	≥8 to ≤256	0
	Cefepime	71	32	64	≥0.12 to ≤64	18.3
	Piperacillin-tazobactam	71	4	32	≥0.5 to ≤256	88.7
	Imipenem	61	0.25	0.5	≥0.12 to ≤2	98.4
	Meropenem	71	0.12	0.12	≥0.015 to ≤1	100
	Colistin	50	0.5	4	≥0.12 to ≤4	90.0
	Tigecycline	71	0.25	0.5	≥0.06 to ≤2	100

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Table II: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against ceftazidime-nonsusceptible isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	N	MIC (mg/L)			% susceptible[b]
			50%	90%	Range	
Citrobacter spp.	Ceftazidime-avibactam	9	0.25	2	≥0.12 to ≤2	100
	Ceftazidime	9	64	256	≥32 to ≤256	0
	Cefepime	9	32	64	≥0.25 to ≤64	22.2
	Piperacillin-tazobactam	9	128	256	≥4 to ≤256	44.4
	Imipenem	9	0.25	2	≥0.12 to ≤2	77.8
	Meropenem	9	0.12	2	≥0.03 to ≤2	88.9
	Colistin	7	0.5	1	≥0.25 to ≤1	100
	Tigecycline	9	0.5	0.5	≥0.12 to ≤0.5	100
Other Enterobacterales[c]	Ceftazidime-avibactam	2	0.5	0.5	≥0.06 to ≤0.5	100
	Ceftazidime	5	16	256	≥8 to ≤256	0
	Cefepime	5	4	64	≥0.5 to ≤64	20.0
	Piperacillin-tazobactam	5	4	128	≥1 to ≤128	80.0
	Imipenem	2	4	4	≥0.5 to ≤4	50.0
	Meropenem	5	0.12	0.25	≥0.06 to ≤0.25	100
	Colistin	2	16	16	≥8 to ≤16	0
	Tigecycline	5	2	4	≥1 to ≤4	60.0
Pseudomonas aeruginosa	Ceftazidime-avibactam	50	8	256	≥2 to ≤256	58.0
	Ceftazidime	55	64	256	≥16 to ≤256	0
	Cefepime	55	32	64	≥2 to ≤64	1.8
	Piperacillin-tazobactam	55	128	256	≥4 to ≤256	10.9
	Imipenem	50	16	16	≥0.5 to ≤16	10.0
	Meropenem	55	4	32	≥0.06 to ≤32	43.6
	Colistin	46	1	2	≥0.5 to ≤4	93.5
Pseudomonas aeruginosa, MBL-negative	Ceftazidime-avibactam	35	4	32	≥2 to ≤256	82.9
	Ceftazidime	40	32	256	≥16 to ≤256	0
	Cefepime	40	16	64	≥2 to ≤64	2.5
	Piperacillin-tazobactam	40	128	256	≥4 to ≤256	15.0
	Imipenem	35	2	16	≥0.5 to ≤16	14.3
	Meropenem	40	1	16	≥0.06 to ≤32	60.0
	Colistin	32	1	2	≥0.5 to ≤4	90.6

[a]Isolates of ceftazidime-nonsusceptible Enterobacterales (N = 259) and *Pseudomonas aeruginosa* (N = 55) were collected in Malaysia as part of the ATLAS program from 2013 to 2019.
[b]Percentage susceptibilities were interpreted according to CLSI breakpoints, except for tigecycline and colistin, which utilised US FDA and EUCAST breakpoints, respectively.
[c]Other Enterobacterales included *Serratia marcescens* (N = 4) and *Proteus mirabilis* (N = 1).

Table II shows the *in vitro* activity of ceftazidime-avibactam and comparator agents against ceftazidime-nonsusceptible isolates of Enterobacterales and *P. aeruginosa*. Among the 259 isolates of Enterobacterales that were ceftazidime-nonsusceptible (24.1% of all Enterobacterales isolates), 96.5% were susceptible to ceftazidime-avibactam (MIC_{90}, 1 mg/L), with MIC_{90} values against individual species or species groups of Enterobacterales ranging from 0.25 mg/L (*E. coli*) to 256 mg/L (*Enterobacter* spp.) and percentages of susceptibility to ceftazidime-avibactam ranged from 88.9% (*Enterobacter* spp.) to 100% susceptible (*E. coli*, *Citrobacter* spp., *S. Marcescens*, and *P. mirabilis*). Compared with ceftazidime-avibactam, the pooled collection of ceftazidime-nonsusceptible Enterobacterales exhibited lower susceptibility rates to the other antimicrobial agents, except for tigecycline (97.3% susceptible; MIC_{90}, 2 mg/L). However, among MBL-negative isolates of ceftazidime-nonsusceptible Enterobacterales, ceftazidime-avibactam exhibited the highest percentage of susceptibility (100%; MIC_{90}, 1 mg/L). Of the 55 isolates of *P. aeruginosa* that were ceftazidime-nonsusceptible (16.6% of all *P. aeruginosa* isolates), 58% were susceptible to ceftazidime-avibactam (MIC_{90}, 256 mg/L). Lower susceptibility rates (from 1.8% [cefepime] to 43.6% [meropenem]) were seen among the other agents included in this study apart from colistin (93.5%; MIC_{90}, 2 mg/L). The percentage of susceptibility to ceftazidime-avibactam was higher among MBL-negative isolates of *P. aeruginosa* (82.9% susceptible; MIC_{90}, 32 mg/L) compared with the pooled isolates of ceftazidime-nonsusceptible *P. aeruginosa*.

Table III depicts the *in vitro* activity of ceftazidime-avibactam and comparator agents against isolates of Enterobacterales and *P. aeruginosa* with a meropenem-nonsusceptible phenotype. Among the 12 isolates of Enterobacterales that were meropenem-nonsusceptible (1.1% of all Enterobacterales isolates), 33.3% were susceptible to ceftazidime-avibactam (MIC_{90}, 256 mg/L). The highest susceptibility was seen with tigecycline (100% susceptible; MIC_{90}, 1 mg/L), followed by colistin (91.7% susceptible; MIC_{90}, 2 mg/L); only 8.3% (MIC_{90}, 16 mg/L) of the

Table III: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against meropenem-nonsusceptible isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	N	MIC (mg/L)			% susceptible[b]
			50%	90%	Range	
Enterobacterales[c]	Ceftazidime-avibactam	12	256	256	≥1 to ≤256	33.3
	Ceftazidime	12	256	256	≥128 to ≤256	0
	Cefepime	12	64	64	≥32 to ≤64	0
	Piperacillin-tazobactam	12	128	256	≥128 to ≤256	0
	Imipenem	12	8	16	≥0.25 to ≤16	8.3
	Meropenem	12	16	32	≥2 to ≤32	0
	Colistin	12	0.25	2	≥0.25 to ≤4	91.7
	Tigecycline	12	0.5	1	≥0.12 to ≤1	100
Enterobacterales, MBL-negative	Ceftazidime-avibactam	4	2	4	≥1 to ≤4	100
	Ceftazidime	4	256	256	256	0
	Cefepime	4	64	64	≥32 to ≤64	0
	Piperacillin-tazobactam	4	128	256	≥128 to ≤256	0
	Imipenem	4	2	4	≥0.25 to ≤4	25.0
	Meropenem	4	2	4	≥2 to ≤4	0
	Colistin	4	0.25	4	≥0.25 to ≤4	75.0
	Tigecycline	4	1	1	≥0.12 to ≤1	100
Pseudomonas aeruginosa	Ceftazidime-avibactam	51	8	256	≥1 to ≤256	60.8
	Ceftazidime	55	16	256	≥1 to ≤256	34.6
	Cefepime	55	16	64	≥1 to ≤64	9.1
	Piperacillin-tazobactam	55	32	256	≥2 to ≤256	38.2
	Imipenem	51	16	16	≥2 to ≤16	0
	Meropenem	55	16	32	≥4 to ≤32	0
	Colistin	46	1	2	≥0.25 to ≤4	97.8
Pseudomonas aeruginosa, MBL-negative	Ceftazidime-avibactam	36	4	32	≥1 to ≤256	86.1
	Ceftazidime	40	8	256	≥1 to ≤256	47.5
	Cefepime	40	8	32	≥1 to ≤64	12.5
	Piperacillin-tazobactam	40	16	256	≥2 to ≤256	52.5
	Imipenem	36	16	16	≥2 to ≤16	0
	Meropenem	40	8	16	≥4 to ≤32	0
	Colistin	32	1	2	≥0.25 to ≤4	96.9

[a]Isolates of meropenem-nonsusceptible Enterobacterales (N = 12) and *Pseudomonas aeruginosa* (N = 55) were collected in Malaysia as part of the ATLAS program from 2013 to 2019.
[b]Percentage susceptibilities were interpreted according to CLSI breakpoints, except for tigecycline and colistin, which utilised US FDA and EUCAST breakpoints, respectively.
[c]Enterobacterales included *Klebsiella pneumoniae* (N = 9), *Enterobacter cloacae* (N = 2), and *Citrobacter koseri* (N = 1).

meropenem-nonsusceptible isolates of Enterobacterales were susceptible to imipenem and none were susceptible to ceftazidime, cefepime, or piperacillin-tazobactam. When only MBL-negative isolates were considered, all isolates were susceptible to ceftazidime-avibactam (100% susceptible; MIC_{90}, 4 mg/L). Among 55 isolates of *P. aeruginosa* that were meropenem-nonsusceptible (16.6% of all *P. aeruginosa* isolates), 60.8% were susceptible to ceftazidime-avibactam (MIC_{90}, 256 mg/L). Apart from colistin (97.8% susceptible; MIC_{90}, 2 mg/L), lower susceptibility rates (from 0% [imipenem] to 38.2% [piperacillin-tazobactam]) were observed with all the other agents included in this study. The percentage of susceptibility to ceftazidime-avibactam was higher among MBL-negative isolates of *P. aeruginosa* (86.1% susceptible; MIC_{90}, 32 mg/L) compared with the pooled isolates of meropenem-nonsusceptible *P. aeruginosa*.

Table IV describes the *in vitro* activity of ceftazidime-avibactam and comparator agents against colistin-resistant isolates of Enterobacterales and *P. aeruginosa*. Among the 22 colistin-resistant isolates of Enterobacterales (2.1% of all Enterobacterales isolates), 100% (MIC_{90}, 1 mg/L) were susceptible to ceftazidime-avibactam, imipenem, and tigecycline. Susceptibility to other agents ranged from 54.5% (ceftazidime) to 95.5% (meropenem). Among 12 colistin-resistant isolates of *P. aeruginosa* (3.6% of all *P. aeruginosa* isolates), 100% (MIC_{90}, 4 mg/L) were susceptible to ceftazidime-avibactam and cefepime. Other agents demonstrated susceptibilities ranging from 75% (ceftazidime and piperacillin-tazobactam) to 91.7% (meropenem). No MBL-positive isolates were detected among colistin-resistant isolates of Enterobacterales and *P. aeruginosa*.

Table V shows the *in vitro* activity of ceftazidime-avibactam and comparator agents against MDR isolates of Enterobacterales and *P. aeruginosa*. MDR is defined in the ATLAS database as resistance to any three of the following groups of antimicrobial agents: cephalosporins, carbapenems, quinolones, aminoglycosides, polymyxins, monobactams, and penicillin combination.[14] The MDR

Table IV: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against colistin-resistant isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	N	MIC (mg/L)			% susceptible[b]
			50%	90%	Range	
Enterobacterales[c]	Ceftazidime-avibactam	22	0.12	1	≥0.03 to ≤2	100
	Ceftazidime	22	4	128	≥0.12 to ≤256	54.5
	Cefepime	22	0.25	32	≥0.12 to ≤64	68.2
	Piperacillin-tazobactam	22	4	64	≥1 to ≤256	81.8
	Imipenem	22	1	1	≥0.12 to ≤1	100
	Meropenem	22	0.06	0.25	≥0.03 to ≤2	95.5
	Colistin	22	4	16	≥4 to ≤16	0
	Tigecycline	22	0.5	1	≥0.12 to ≤2	100
Pseudomonas aeruginosa	Ceftazidime-avibactam	12	2	4	≥1 to ≤8	100
	Ceftazidime	12	2	16	≥1 to ≤16	75.0
	Cefepime	12	2	4	≥2 to ≤8	100
	Piperacillin-tazobactam	12	8	32	≥4 to ≤64	75.0
	Imipenem	12	2	4	≥0.5 to ≤8	83.3
	Meropenem	12	0.5	2	≥0.25 to ≤4	91.7
	Colistin	12	4	8	≥4 to ≤8	0

[a]Isolates of colistin-resistant Enterobacterales (N = 22) and *Pseudomonas aeruginosa* (N = 12) were collected in Malaysia as part of the ATLAS program from 2013 to 2019. None of the colistin-resistant isolates were MBL-positive.
[b]Percentage susceptibilities were interpreted according to CLSI breakpoints, except for tigecycline and colistin, which utilised US FDA and EUCAST breakpoints, respectively.
[c]Enterobacterales included *Enterobacter* spp. (N = 11), *Escherichia coli* (N = 8), and *Klebsiella pneumoniae* (N = 3). *Proteus* spp. and *Serratia* spp. were excluded as they are intrinsically resistant to colistin.

Table V: *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against MDR isolates of Enterobacterales and *Pseudomonas aeruginosa*[a]

Organism	Antimicrobial agent	N	MIC (mg/L)			% susceptible[b]
			50%	90%	Range	
Enterobacterales[c]	Ceftazidime-avibactam	279	0.25	1	≥0.015 to ≤256	97.1
	Ceftazidime	286	32	256	≥0.06 to ≤256	21.0
	Cefepime	286	32	64	≥0.12 to ≤64	22.4
	Piperacillin-tazobactam	286	8	256	≥0.25 to ≤256	65.7
	Imipenem	279	0.25	2	≥0.06 to ≤16	90.0
	Meropenem	286	0.06	0.25	≥0.015 to ≤32	95.8
	Colistin	221	0.5	4	≥0.12 to ≤16	89.1
	Tigecycline	286	0.5	2	≥0.06 to ≤8	96.2
Pseudomonas aeruginosa	Ceftazidime-avibactam	38	32	256	≥2 to ≤256	44.7
	Ceftazidime	39	256	256	≥4 to ≤256	10.3
	Cefepime	39	32	64	≥4 to ≤64	10.3
	Piperacillin-tazobactam	39	128	256	≥16 to ≤256	7.7
	Imipenem	38	16	16	≥1 to ≤16	21.1
	Meropenem	39	16	32	≥0.5 to ≤32	18.0
	Colistin	36	1	2	≥0.5 to ≤2	100

[a]MDR isolates of Enterobacterales (N = 286) and *Pseudomonas aeruginosa* (N = 39) were collected in Malaysia as part of the ATLAS program from 2013 to 2019. According to the ATLAS database, MDR is defined as resistance to any three of the following groups: cephalosporins, carbapenems, quinolones, aminoglycosides, polymyxins, monobactams, and penicillin combination (i.e., piperacillin-tazobactam).
[b]Percentage susceptibilities were interpreted according to CLSI breakpoints, except for tigecycline and colistin, which utilised US FDA and EUCAST breakpoints, respectively.
[c]Enterobacterales included *Klebsiella pneumoniae* (N = 143), *Escherichia coli* (N = 98), *Enterobacter* spp. (N = 24), *Proteus* spp. (N = 11), *Citrobacter* spp. (N = 9), and *Serratia marcescens* (N = 1).

phenotype was present in 286 (26.7%) of all Enterobacterales isolates. Among these, 97.1% were susceptible to ceftazidime-avibactam (MIC_{90}, 1 mg/L). Lower susceptibility rates were observed with all other antibacterials included in this study—from 21% (ceftazidime) to 96.2% (tigecycline). Separately, the MDR phenotype was present in 39 (11.7%) *P. aeruginosa* isolates. Ceftazidime-avibactam demonstrated a percentage of susceptibility of 44.7% (MIC_{90}, 256 mg/L), which was higher than that observed for all other agents except colistin (100% susceptible; MIC_{90}, 2 mg/L).

DISCUSSION

This study reports the *in vitro* antimicrobial susceptibility and the prevalence of resistant phenotypes among clinical isolates of Enterobacterales and *P. aeruginosa* collected in Malaysia from 2013 to 2019. Among Enterobacterales isolates, the highest percentages of susceptibility were seen with ceftazidime-avibactam (99.2%), meropenem (98.9%), and tigecycline (96.9%). The reduced percentage of susceptibility of colistin in the pooled Enterobacterales group is attributed to the presence of 73 isolates of *Proteus* spp. and 52 isolates of *Serratia* spp., which are intrinsically resistant to colistin (Table I).[15] When these bacterial species were excluded from the pooled Enterobacterales group, colistin demonstrated a percentage of susceptibility of 96.5%. Separately, *P. aeruginosa* isolates demonstrated the highest susceptibilities to colistin (95.6%), followed by ceftazidime-avibactam (93.1%) and cefepime (87.1%) (Table I).

In Malaysia, there are limited data on the *in vitro* activity of ceftazidime-avibactam against clinical isolates of Enterobacterales and *P. aeruginosa*. However, the recent 2015–2017 INFORM study (which included Asia-Pacific countries such as Australia, Japan, South Korea, Malaysia, Philippines, Taiwan, and Thailand) found that Enterobacterales and *P. aeruginosa* also displayed the highest susceptibility rates to ceftazidime-avibactam, colistin, and meropenem. In the INFORM study, 98.1% and 97.7% of Enterobacterales isolates were susceptible to ceftazidime-avibactam and meropenem, respectively. Among isolates of *P. aeruginosa*, 99.7% and 92.7% were susceptible to colistin and ceftazidime-avibactam, respectively.[8]

Specific to Malaysia, isolates of Enterobacterales collected from Asia-Pacific countries as part of the 2012–2015 INFORM programme exhibited a percentage of susceptibility of 99.7% to ceftazidime-avibactam; of note, this value is comparable to the rate of susceptibility reported in this study (99.2%). Across the Asia-Pacific countries studied, the percentage of susceptibility of Enterobacterales isolates to ceftazidime-avibactam ranged from 97% (Philippines) to 100% (Hong Kong and Korea). Ceftazidime-avibactam demonstrated a 94.7% susceptibility against isolates of *P. aeruginosa* collected in Malaysia, slightly higher (1.6%) compared with the rate of susceptibility in this study. Percentages of susceptibility ranged from 83.1% (Thailand) to 100% (Hong Kong) across the Asia-Pacific countries.[16]

It is important to consider MBL-producing isolates when evaluating the *in vitro* activity of ceftazidime-avibactam against clinical isolates of Enterobacterales and *P. aeruginosa*. In this study, the resistance of Enterobacterales isolates to ceftazidime-avibactam was only observed in eight isolates (0.8% [8/956] of all ceftazidime-avibactam-tested isolates), all of which were MBL-positive. All MBL-negative isolates of Enterobacterales, including resistant subsets of Enterobacterales isolates (i.e. ceftazidime-nonsusceptible, meropenem-nonsusceptible, and colistin-resistant phenotypes) (Table I-IV), were susceptible to ceftazidime-avibactam. This susceptibility may be attributed to the broad-spectrum coverage of ceftazidime-avibactam, which effectively inhibits Ambler Class A, C, and D.[7] In this study, 21 isolates (6.9% [21/303] of all ceftazidime-avibactam-tested isolates) of *P. aeruginosa* were resistant to ceftazidime-avibactam; 15 of which were MBL-positive. MBL-negative isolates of *P. aeruginosa* exhibited a 4.8% higher susceptibility (97.9%) to ceftazidime-avibactam compared with the pooled collection of *P. aeruginosa*. This result is consistent with that reported in the Asia-Pacific 2012–2015 INFORM study.[16]

Among resistant subsets in this study, tigecycline exhibited high percentages of susceptibility against ceftazidime-nonsusceptible (97.3%), meropenem-nonsusceptible (100%), and colistin-resistant (100%) isolates of Enterobacterales, whereas colistin demonstrated the highest percentages of susceptibility among ceftazidime-nonsusceptible (93.5%), meropenem-nonsusceptible (97.8%), and MDR (100%) isolates of *P. aeruginosa*. These outcomes were expected as tigecycline and colistin are widely recognised as 'last resort antibiotics' and remain highly active against carbapenem-resistant and MDR isolates.[17–19] However, there are growing reports of carbapenem and colistin resistance in Southeast Asia,[1] making ceftazidime-avibactam an important addition to the antimicrobial armamentarium. One study investigating the efficacy of ceftazidime-avibactam versus colistin for CRE infections revealed that ceftazidime-avibactam was associated with a 64% probability of better outcome (95% confidence interval, 57%–71%) compared with colistin.[20]

The increased prevalence of MDR isolates is a growing issue despite continuous efforts to increase awareness of antibiotic resistance.[21] In this study, MDR isolates accounted for 26.7% of all Enterobacterales isolates. Alarmingly, this is much higher than MDR Enterobacterales rates reported in the INFORM study, where only 9.1% of the isolates collected from Malaysia were identified as MDR. Furthermore, the rates of MDR Enterobacterales isolates ranged from 2.7% (Australia) to 19.4% (Thailand) across the Asia-Pacific countries studied.[16]

Among *P. aeruginosa* isolates in this study, 11.7% were MDR. According to the results from the Asia-Pacific 2012–2015 INFORM study, only 7.1% of *P. aeruginosa* isolates collected in Malaysia were MDR, while rates of MDR *P. aeruginosa* in other Asia-Pacific countries varied between 5.7% (Australia) and 24% (Philippines).[16] In this study, ceftazidime-avibactam remained the most active agent (97.1%) against MDR isolates of Enterobacterales and second most active agent (44.74%), after colistin, against MDR isolates of *P. aeruginosa*. It is important to note that the isolates collected from Malaysia in the Asia-Pacific 2012–2015 and 2015–2017 INFORM studies were included in this study as well.

One of the limitations of this study is the low number of isolates collected over the 7-year period, which may be insufficient to establish the prevalence of resistant subsets in Malaysia. Furthermore, antibacterial surveillance data were not collected from Malaysia in the year 2017 and were not available in the ATLAS database. This gap year makes it difficult to establish the prevalence and pattern of antibiotic resistance over time. In addition, the use of ceftazidime-avibactam was not yet approved in Malaysia when the data was collected (2013–2019), and thus the local resistance pattern of ceftazidime-avibactam cannot be determined as there had not been clinical usage in the country. Nevertheless, as there have been limited antimicrobial surveillance studies in Malaysia that reports susceptibility data of antibiotics, the results of this study will serve as a valuable resource to inform healthcare professionals of the local antimicrobial activities of commonly used antibiotics and to guide their optimal use. With its recent entry into the Malaysian healthcare system, more susceptibility data on the use of ceftazidime-avibactam among Enterobacterales and *P. aeruginosa* will be available in the near future.

CONCLUSION

Clinical isolates of Enterobacterales and *P. aeruginosa* collected from hospitals in Malaysia from 2013 to 2019 were highly susceptible to ceftazidime-avibactam. Additionally, ceftazidime-avibactam consistently displayed comparable, and often, higher percentages of susceptibility as compared with meropenem at all outcome measures. This shows that ceftazidime-avibactam is a valuable alternative to carbapenems. Ceftazidime-avibactam exhibited potent *in vitro* activity against MBL-negative isolates of Enterobacterales and *P. aeruginosa*, including isolates with ceftazidime-nonsusceptible, meropenem-nonsusceptible, and colistin-resistant phenotypes, making it a potential alternative to last-resort antimicrobial agents such as colistin and tigecycline. Furthermore, ceftazidime-avibactam demonstrated the highest percentage of susceptibility against MDR isolates of Enterobacterales. Based on the potent *in vitro* activity of ceftazidime-avibactam in Malaysia, and its established clinical efficacy,[22–26] ceftazidime-avibactam should be considered in the treatment of indicated infections caused by susceptible strains of aerobic Gram-negative pathogens.

DECLARATION OF CONFLICT OF INTEREST

Salvinder S, Chen VSY are employees of Pfizer Malaysia Sdn Bhd.

ETHICAL APPROVAL

Individual patient's informed consent was not required as this study was an antimicrobial surveillance programme (NMRR-18-1271-39749). Ethical approval for this study was obtained from MREC, Ministry of Health Malaysia.

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Increased incidence and aetiological factors of back pain among Universiti Malaysia Sabah staff and undergraduates during the COVID-19 lockdown period

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ABSTRACT

Introduction: In response to the coronavirus disease 2019 (COVID-19) pandemic, many countries have introduced work from home campaigns. Most teaching faculties have moved to an online delivery mode, which could put students and teachers at risk of back pain. The aim of this study was to determine the frequency of newly diagnosed back pain among lecturers and undergraduates from a tertiary education centre during the COVID-19 lockdown and to identify the possible factors associated with this back pain.

Materials and Methods: This study was a cross-sectional survey conducted among 1,500 lecturers and students of Universiti Malaysia Sabah (UMS). The questionnaire used was modified from previous studies on back pain.

Results: There were 346 newly diagnosed cases of back pain among students and lecturers of UMS. More than half of the participants (61.2%) suffered lower back pain in the lumbar region. There was a significant correlation between increased time of sitting and reduced exercise time, and the incidence of back pain. Poor ergonomic sitting conditions and poor perceived health conditions during the lockdown period also had a significant impact on the frequency of back pain.

Conclusion: The university community has undergone a significant increase in sitting time and a decrease in exercise time during the lockdown. This has contributed to an increase in the frequency of back pain. It is recommended that further studies be done to guide the university community regarding the maintenance of exercise and management of sitting hours, in order to reduce the frequency of back pain.

KEYWORDS:
Back pain, COVID-19 lockdown

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) emerged at the end of December 2019 in China.[1] The authorities in China took an unprecedented step in locking down parts of China to lower the risk of further disease transmission.[2]

The spread of COVID-19, however, was soon discovered in other parts of the world, and the World Health Organization (WHO) soon declared it to be a pandemic.[3] In response to the pandemic, many countries, including Malaysia, have introduced travel restrictions, social distancing, self-isolation, lockdowns, and work from home campaigns. As of March 25, 150 countries have closed their schools and educational institutions nationwide, impacting over 80% of the world's students and teachers.[4]

Most teaching faculties have moved to an online delivery mode in response to this. Although online teaching is not a new concept, it has never been an inclusive mode entirely, especially in medical education. This mode of teaching involves increased screen time and sitting, which could be a risk factor for back pain.[5]

Back pain may be caused by a number of diverse factors. It may originate from disease, injuries, or stresses in many different structures, including the bones, muscles, ligaments, joints, nerves, or spinal cord. Often, the aetiology of the pain lies not only in terms of the pain itself but also in the way we stand, sit, rest, and play. Posture has a direct impact on the extent to which back pain occurs; research among patients suffering from back pain shows that 85% of all problems can be traced back to a long-term incorrect sitting position.[6]

About 70% of adults have suffered from back pain at least once in their lives.[7] In Malaysia, the prevalence of back pain was found to be 12%.[8] However, no study on back pain has been conducted in Malaysia during the COVID-19 lockdown period.

The aim of this study was to determine the frequency of newly diagnosed back pain among lecturers and undergraduates of UMS during the COVID-19 lockdown and to identify the possible factors associated with this back pain. Our research hypothesis is that there will be an increase in back pain during the lockdown period, compared to that before the lockdown.

MATERIALS AND METHODS

A cross-sectional survey was conducted among lecturers and students of UMS. Convenience sampling was utilised. Online questionnaires were distributed to 1,500 lecturers and students via an Internet-based application. The questionnaire used was modified from previous studies on back pain based on the local setting and culture.[9,10] Content

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validity after modification was ensured through a focus group discussion that included clinical and academic experts in the field. All experts had more than five years of experience and will be in possession of a postgraduate qualification.

The questionnaire was organised into three parts: part one consisted of socio-demographic information, part two content included details of current changes in lifestyle due to the lockdown, and part three collected information regarding the characteristics of the pain. This included a self-assessment regarding the participants ergonomic conditions, medication for pain, exercise hours, sitting hours, and perceived health before, after, and during the lockdown. This study adopted a purposive sampling and lasted for six months. The pain score was categorised into three levels: mild (1–3), moderate (4–6), and severe (7 and above).

The questionnaire was pre-tested on 10 students before distributing it to the other subjects to ensure that the questionnaire was easily understood. After obtaining ethical clearance, the questionnaire was created online and distributed using a chat application. A cover letter was used to inform the participants of the purpose of the study and assure the anonymity and the entitlement of the respondents to complete or decline the survey questionnaire. The questionnaire was distributed for one week in early May 2020, which is six weeks after the COVID-19 lockdown in Malaysia.

Lecturers and students of UMS who were actively involved in teaching and learning during the pandemic period were eligible for inclusion of this study. Exclusion criteria were students with known spinal deformities, such as scoliosis, spondylolisthesis, spondylosis, spondylolysis, spinal stenosis, prolapsed intervertebral disc or any neurological deficit, and history of back pain before the COVID-19 quarantine.

Informed consent was inferred by voluntary completion and return of the questionnaire. Statistical analysis of the data was performed using SPSS software version 20.

RESULTS

After the distribution of 1,500 questionnaires, 842 responded to the survey. The response rate was 56.1%. However, only 346 participants fulfilled the criteria of newly diagnosed back pain.

Demography

Table I shows the demography of the participants. There were 346 newly diagnosed cases of back pain among students and lecturers of UMS. The average age of participants was 25.83 ± 8.88 years. There were 156 (45.1%) male participants and 190 (54.9%) female participants. More than half of the participants (61.2%) suffered lower back pain in the lumbar region. Of the participants who had lower back pain, 122 were females (57.5%), and 90 (42.5%) were males. Most participants (93.6%) reported a bad ergonomic condition of their chairs.

Impact of hours of physical activity and sitting hours on the frequency of back pain

A paired sample t-test indicates that there is a significant difference in some of the study variables, including exercise hours, sitting hours, and lower back pain before and after the lockdown. Exercise hours significantly decreased ($p < 0.001$; 95% CI = 2.731–2.910), from 3.16 ± 0.90 hours to 0.34 ± 0.48 hours. Correspondingly, sitting hours significantly increased ($p < 0.001$; 95% CI = –[2.774–2.590]), from 2.20 ± 0.45 hours to 4.88 ± 1.00 hours. Similarly, mean lower back pain increased from absent to mild (2.88 ± 0.86; $p < 0.001$; 95% CI = –[2.975–2.788]).

The Wilcoxon signed-rank test showed a significant difference ($p < 0.001$) in perceived health condition before and after the lockdown. The mean perceived health deteriorated from moderate (2.95 ± 0.23) to poor (1.63 ± 0.48). These data are presented in Table II.

Linear regression analysis (Table III) showed that the number of hours spent on physical activity significantly explains 2.0% of the variance in back pain ($F[1,344] = 7.892$; $p < 0.01$). The findings also reported $\beta = 0.150$ and 95% CI = 0.083–0.469, indicating that the number of hours spent on physical activity also significantly influence back pain.

Long sitting times significantly explained 6.3% of the variance in back pain ($F[1,344] = 24.334$; $p < 0.001$). The results showed that $\beta = 0.257$ and 95% CI = 0.137–0.319, indicating that the long hours of sitting significantly influence back pain.

Impact of ergonomic sitting conditions and perceived health conditions on the frequency of back pain

Binary logistic regression analysis (Table IV) indicated that people with poor ergonomic sitting conditions are about two times more likely to experience mild back pain compared to people with good ergonomic sitting conditions (odd ratio = 2.045; 95% CI = 1.177–3.583). In addition, participants with bad perceived health condition are two times more likely to experience moderate back pain compared to participants with good perceived health condition (odd ratio = 2.489; 95% CI = 1.765–3.511).

DISCUSSION

Back pain is among the most frequent reasons for visiting a doctor in Europe,[11,12] and the burden of illness from this problem is significant. The prevalence of back pain in developed countries is estimated to range from 10% to 31%.[13,14] In Malaysia, the prevalence of back pain was 12%, rated as the ninth and fifth most common complaint in public and private primary healthcare clinics, respectively.[15] However, to date, no data is available regarding back pain of university staff and students in Malaysian universities. Prevention strategies for back pain can only be successful if the associated risk factors are identified and better understood.[16]

There are several diverse risk factors associated with back pain,[17] including gender, age, posture, smoking, psychological factors, general health status, duration of

Table I: Demography of participants (n = 346)

Variables	
Pain location	**n (%)**
Cervical	99 (28.6)
Thoracic	32 (9.2)
Lumbar	215 (62.1)
Medication for pain	**n (%)**
Yes	21 (6.1)
No	323 (93.4)
Age	Mean ± SD 25.83 ± 8.88
Gender	**n (%)**
Male	156 (45.1)
Female	190 (54.9)
Ergonomic condition	**n (%)**
Good	22 (6.4)
Bad	324 (93.6)

Table II: Difference in study variables before and during lockdown (n = 346)

	Mean ± SD		p	CI
	p Before lockdown	CI During lockdown		
Exercise hours [a]	3.16 ± 0.90	0.34 ± 0.48	< 0.001	2.731–2.910
Sitting hours [a]	2.20 ± 0.45	4.88 ± 1.00	< 0.001	–(2.774–2.590)
Perceived health [b]	2.95 ± 0.23	1.63 ± 0.48	< 0.001	-
Low back pain [a]	0.00 ± 0.00	2.88 ± 0.86	< 0.001	–(2.975–2.788)

[a] Paired sample t-test
[b] Wilcoxon signed-rank test

Table III: Linear regression analysis of the association between exercise and sitting hours (n = 346)

During lockdown	R2	β	α	CI
Exercise hours	0.020	0.150	0.005	0.083–0.469
Sitting hours	0.063	0.257	0.000	0.137–0.319

Table IV: Binary logistic regression analysis of the association between poor ergonomic condition and bad perceived health (n = 346)

	Risk estimate (CI)		
	Mild pain	Moderate pain	α
Poor ergonomic condition	2.054 (1.177–3.583)	0.398 (0.276–0.574)	0.000
Bad perceived health	0.676 (0.572–0.798)	2.489 (1.765–3.511)	0.000

computer usage, physical activity levels, and history of prior back pain. However, there are no specific risk factors identified for back pain during the current pandemic in Malaysia.

The study showed significant demographic differences in terms of gender. The female respondents were found to have a higher incidence of back pain. This finding is consistent with other studies that found similar gender differences.[14,18,19]

Our study also showed that the majority of respondents had lumbar back pain (62.1%), followed by pain in the cervical and thoracic areas. This echoes the results from a study in Saudi Arabia during the COVID-19 lockdown period.[20] This was due to excessive sitting involved in taking online classes, working on assignments, preparing lectures, and conducting online meetings. Studies showed that the use of computers for five or more hours a day showed a significant association with back pain in students.[21,22]

Studies have shown that with adequate exercise time, pain can be reduced.[23,24] Previous reviews have discussed the success of increasing home exercise and back health education in reducing back pain.[25,26] The study shows that exercise hours were reduced significantly during the lockdown period. This was anticipated due to the closure of

exercise areas and social distancing protocols. This problem has significantly increased the frequency of back pain.

LIMITATIONS

Although this study offers valuable information regarding patients with back pain during the lockdown period, some important limitations should be considered when interpreting these findings. This study recruited participants from a university in Malaysia, and the participants are predominantly people with higher formal education, thus limiting the generalizability to a broader population of patients with back pain across the country. This, therefore, does not represent the back pain problem among the general population of Malaysia. In addition, it should be acknowledged that our study participants had online access, as the survey required Internet connection. Thus, this study may not provide adequate representation of individuals who do not have as much access to technology.

CONCLUSION

The use of computers is at its peak during this lockdown period. Our study showed that the university community has undergone a significant increase in sitting time and a decrease in exercise time during the lockdown. This has contributed to an increase in the frequency of back pain. It is recommended that further studies be done to guide the university community regarding the maintenance of exercise and management of sitting hours, in order to reduce the frequency of back pain. We are in the process of planning a Back Pain Module for our staff and students, in order to reduce back pain during this period. This module will include non-pharmacological methods, such as basic exercises and ergonomic knowledge.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Identification of warning signs in Malaysian patients having COVID-19 infection who progress to severe form of the illness

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus, now widely known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused 3 major pandemic waves in Malaysia. We aimed to identify the warning signs as indicators that predict the progression of disease.

Materials and Methods: This is a retrospective cohort study of adult patients more than 12 years of age presenting with laboratory-confirmed COVID-19 admitted in three separate hospitals around the country.

Results: Of the 228 patients initially admitted with mild illness, 47 had progressed requiring oxygen. The median time from admission to deterioration was 3 days (IQR 2 - 5). Age more than ≥50years old (median age = 42.5, IQR = 28.8 – 57.0), higher temperature (mean = 37.3, IQR 36.8 - 38.0), MEWS score >3 (9, 19.1%), Neutrophil-to-lymphocyte ratio (NLR) >3.13 , (18, 38.3%) C-reactive protein (CRP) >5. (12, 27.3%), multiple zonal involvement on the chest radiography on admission (2, IQR 1-3) were more common in the deteriorated group on admission. On multivariate analysis, multiple comorbidities (HR = 7.40, 95 percent CI 2.58–21.2, p0.001), presence of persistent fever (HR = 2.88, 95 percent CI 1.15 – 7.2, p = 0.024), MEWS scoring >3 (HR of 6.72 ;95 percent CI 2.81–16.0, p0.001) were associated with progression to severe illness.

Conclusion: In our cohort, we found that several factors were associated with the severity of COVID19. Early detection of these factors could correctly identify patients who need more intensive monitoring, and early referral for ICU care.

KEYWORDS:
COVID-19, Severe pneumonia, Risk factors, Progression

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, which is now widely known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In January 2020, Malaysia had the first family cluster of COVID-19 among travellers arriving from Wuhan, China. Following that, the initial cluster of cases were among Malaysians or foreigners who had strong epidemiological links from affected countries. Reported cases and person-to-person transmission within the community remained relatively low, until large clusters of cases began to emerge in March, with the largest cluster linked to a mass religious gathering. Consequently, a spike in local cases and exportation of cases to neighbouring countries occurred. Since then, Malaysia has seen three waves with the largest being the third wave, and to date, it has recorded 2,699240 cases with a total of 30,956 deaths and a fatality rate of 1.1%.

The search for an antiviral began very early on in the pandemic with studies looking at repurposing drugs with antiviral activity. Evidence has not been very favourable so far, and most of these drugs have yet to be approved for use outside of a clinical trial. WHO Solidarity Trial found that the repurposed drugs had little or no effect on hospitalised patients in terms of reducing overall mortality, initiating ventilation, or reducing hospital stay. Remdesivir, however, has been licenced for use in the European Union for the treatment of COVID-19 in hospitalised patients who require supplementary oxygen following the NIH clinical trial results. In recent times, favourable trial results of novel antiviral agents by two leading pharmaceutical companies have led to a race in procuring these medications by government agencies in the hope to reduce hospitalisation and intensive care unit (ICU) care.

Vaccination efforts offer the best evidence in terms of prevention, reducing hospitalisations and preventing severe disease. However, as primary and booster vaccination efforts

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are being rolled out worldwide, countries are seeing a rapid rise in cases being reported with increasing hospitalisation owing to lack of adherence to preventive measures, such as social distancing and wearing of masks in public, antivaccine drive, and the emergence of variants of concern. Although a large percentage of patients present with mild illness, the risk factor for mortality and severe illnesses is markedly increased in patients greater than 50 years of age and who have more than one non-communicable disease. This was also seen in other studies where older age, smoking, and underlying comorbidities, such as diabetes mellitus, hypertension, and cardiac/lung diseases, were reported as risk factors for severe illness.

Early recognition of patients who are at high risk of developing more severe disease is still very relevant in times of an overwhelmed medical system. Due to the high mortality and morbidity rate, clinicians tend to be very cautious in their management of even mildly symptomatic patients. The lack of access to available antivirals would prompt physicians to overtreat patients in the high-risk groups, even if they present with mild symptoms and show no signs of deterioration leading to overuse of Personal Protective Equipment's (PPE) and exposing patients to drug side effects. The opposite is also true, that these warning signs can guide us to identify the patients who need more intensive monitoring as well as to facilitate early referral for ICU care.

At present, there is an urgent need for us to recognise the warning signs as indicators that predict the progression of disease so that we could correctly identify patients who need more intensive monitoring and early referral for ICU care. The fundamental goal of this research is to reduce mortality and morbidity, provide adequate care, and improve the efficiency of the healthcare system.

MATERIALS AND METHODS

Patient Selection

This is a retrospective cohort study of patients greater than 18 years of age presenting with laboratory-confirmed COVID-19 admitted in three separate hospitals in Malaysia that have been designated to be COVID-19 treating centres – Hospital Sungai Buloh, Selangor; Hospital Lahad Datu, Sabah; and Hospital Melaka, Melaka. The study included patients who were admitted with confirmed COVID-19 illness and did not require oxygen at the time of admission between January 25 and April 30, 2020. Patients requiring oxygen on admission were excluded from the study. Clinical diagnosis and classifications were made according to the Malaysian Management Guidelines for COVID-19, version 5.0. According to the guidelines, COVID-19 patients are classified into five categories: (1) asymptomatic, (2) symptomatic with no pneumonia, (3) pneumonia but not requiring oxygen, (4) pneumonia requiring oxygen, and (5) critically ill patients requiring non-invasive or invasive ventilation or in shock. Laboratory confirmation was based on the presence of SARS-CoV-2 in respiratory specimens using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay by the hospital laboratory.

Patients were followed till they reached the outcome of deterioration: Clinically deteriorating to categories 4 and 5 is defined as development of hypoxia with clinical (respiratory rate >20 breath/min and SpO2< 95% or PaO2/FiO2 ratio <300 mmHg) and radiological evidence of worsening pneumonia. For patients who did not deteriorate and remained as mild disease, parameters were collected till day 10 of illness. Patients were followed up till day 10 of illness based on evidence from literature review that suggested the median duration from illness onset to dyspnoea was 7 to 8 days and the current national and WHO guidelines that advocate discharge from COVID-19 care pathway at day 10 of illness., Upon admission, all the patients received standard monitoring and treatment according to the Management Guidelines for COVID-19, version 5.0.

Data Collection

A dedicated team of doctors extracted patient data from the COVID-19 RedCap database (Research Electronic Data Capture) of the three major hospitals. Missing information was traced from hospital electronic records and the patient's manual records. A standardised data collection sheet was used to extract data from RedCap/ manual records, and later, the information was transferred to an excel sheet. Baseline demographic data, clinical symptoms, chronic comorbidities, and vital signs were extracted from the available records using a standardised data collection form. Modified Early Warning Signs (MEWS) scoring was retrieved from the manual notes, which was calculated in real time by skilled nurses during patient review. During the data collection process, this was confirmed by a physician or a trained medical officer to double-check the previously entered numbers. All laboratory and clinical variables were collected at admission, 48 hours before outcome, 24 hours before outcome, and on the day of outcome. Because various patients had a different number of inputs, the poorest vital sign over the previous 24 hours was chosen for analysis.

The chest radiographs were extracted from the hospital picture archiving and communication system (PACS), and reporting was done by a radiologist (with more than nine years of experience), using Digital Imaging and Communications in Medicine (DICOM) images, viewed with a medical-grade monitor system. The findings include the presence or absence of ground-glass opacities, consolidations, reticulations, and/or pleural effusion, as well as the number of total zones involved.

Definitions

Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock. Fever was defined as an axillary temperature of at least 37.3 degrees Celsius. A lower fever threshold was chosen in order to accommodate for fever threshold in older people as well as to account for the practice of using forehead scanners in wards for detecting temperature.

Modified Early Warning Score (MEWS) is a tool that can be used to detect patients who are clinically deteriorating. The Principle of MEWS is based on the subtle changes in several parameters (Blood Pressure/Pulse Rate/Glasgow Coma Scale/Respiratory Rate) as well as large changes within a

Table I: Clinical presentations of patients with COVID-19 on admission

	Total (n=228)	Stable (n=181)	Deteriorated (n=47)	P-value
Age	42.50 (28.75, 57.00)	38.00 (26.00, 54.00)	57.00 (44.50, 62.50)	< 0.001***
Age ≥ 50	85 (37.3%)	55 (30.4%)	30 (63.8%)	< 0.001***
Male	143 (62.7%)	114 (63.0%)	29 (61.7%)	0.867
Active smoker	24 (11.7%)/23	22 (13.2%)/14	2 (5.3%)/9	0.263
Comorbidity				0.001**
No comorbidity	130 (57.0%)	114 (63.0%)	16 (34.0%)	
1 comorbidity	49 (21.5%)	35 (19.3%)	14 (29.8%)	
≥2 comorbidities	49 (21.5%)	32 (17.7%)	17 (36.2%)	
Days of illness on admission	5.00 (3.00, 8.00)/1	5.00 (3.00, 7.00)/1	6.00 (4.00, 8.00)/0	0.062
Days of illness at outcome	11.00 (10.00, 11.00)/1	11.00 (10.00, 11.00)/1	10.00 (8.00, 12.00)/0	0.036
Days of admission at outcome	5.00 (3.00, 7.00)/1	5.000 (3.000, 8.000)/1	3.00 (2.00, 5.00)/0	< 0.001***
Symptom				
Fever	117 (51.3%)	82 (45.3%)	35 (74.5%)	< 0.001***
Cough	152 (66.7%)	116 (64.1%)	36 (76.6%)	0.120
Sore throat	64 (28.1%)	52 (28.7%)	12 (25.5%)	0.719
Fatigue	19 (8.3%)	12 (6.6%)	7 (14.9%)	0.079
Shortness of breath	21 (9.2%)	12 (6.6%)	9 (19.1%)	0.019*
Haemoptysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Anorexia	2 (0.9%)	1 (0.6%)	1 (2.1%)	0.371
Headache	12 (5.3%)	9 (5.0%)	3 (6.4%)	0.716
Diarrhoea	25 (11.0%)	17 (9.4%)	8 (17.0%)	0.186
Nausea	7 (3.1%)	7 (3.9%)	0 (0.0%)	0.350
Vomiting	9 (3.9%)	6 (3.3%)	3 (6.4%)	0.396
Nasal congestion	24 (10.5%)	21 (11.6%)	3 (6.4%)	0.426
Myalgia	17 (7.5%)	8 (4.4%)	9 (19.1%)	0.002**
Signs				
Temperature (°C),	36.80 (36.50, 37.00)	36.80 (36.50, 37.00)	37.30 (36.80, 38.00)	< 0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)	20.00 (18.00, 20.00)	20.00 (18.00, 20.00)	0.391
MEWS score	0.00 (0.00, 1.00)	0.000 (0.00, 1.00)	1.00 (0.00, 2.00)	< 0.001***
MEWS >3	16 (7.0%)/1	7 (3.9%)/1	9 (19.1%)/0	0.001**
Investigation				
NLR >3.13 cells/μL	50 (22.2%)/3	32 (18.0%)/3	18 (38.3%)/0	0.005**
CRP >5 mg/dL	21 (11.9%)/51	9 (6.8%)/48	12 (27.3%)/3	< 0.001***
Chest radiography: total zone involvement	1.00 (0.00, 2.00)/51	0.00 (0.00, 1.00)/42	2.00 (1.00, 3.00)/9	< 0.001***

* P-value < 0.05
** P-value < 0.01
*** P-value < 0.001
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

Table II: COVID-19 patient clinical parameters at 48 hours prior to severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.60, 37.00)/57	36.80 (36.50, 37.00)/38	37.25 (37.00, 37.85)/19	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/55	20.00 (18.00, 20.00)/36	20.00 (18.75, 20.00)/19	0.462
Investigation				
NLR >3.13 cells/μL	17 (25.4%)/161	11 (22.4%)/132	6 (33.3%)/29	0.364
CRP >5 mg/dL	11 (19.6%)/172	6 (14.6%)/140	5 (33.3%)/32	0.142
Chest radiography: total zone involvement‡	1.00 (0.00, 2.00)/200	0.500 (0.00, 2.00)/161	2.00 (1.00, 3.00)/39	0.035*
MEWS score‡	1.00 (0.00, 2.00)/200	0.50 (0.00, 2.00)/161	2.00 (1.00, 3.00)/39	0.035

* P-value < 0.05
*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

single variable during clinical deterioration. An increasing score or a score of more than three is associated with an increased likelihood of death or ICU care.

Statistical Analysis

Patients aged above 18 years and presented with mild illness (less than stage 4) on presentation in the designated COVID-19 treating hospitals were included and de-identified for this analysis. No imputation was done on missing data, and the numbers were reported after slash in the table. Continuous variables were reported as median with interquartile range, and categorical variables were reported as frequency and percentages. Mann–Whitney U test and Fisher's exact test were used respectively to compare differences between the

Table III: COVID-19 patient clinical parameters at 24 hours prior to severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.60, 37.00)/110	36.80 (36.50, 37.00)/95	37.15 (36.98, 37.88)/15	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/28	19.00 (18.00, 20.00)/14	20.00 (19.00, 20.00)/14	<0.001***
Investigation				
NLR >3.13 cells/μL	23 (29.9%)/151	15 (25.0%)/121	8 (47.1%)/30	0.131
CRP >5 mg/dL	13 (19.1%)/160	7 (13.5%)/129	6 (37.5%)/31	0.063
Chest radiography: total zone involvement‡	1.00 (0.00, 3.00)/199	1.00 (0.00, 1.25)/161	3.00 (2.00, 4.00)/38	0.002**

** Pvalue <0.01
*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

Table IV: COVID-19 patient clinical parameters on the day of developing severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.70, 37.00)/108	36.80 (36.60, 37.00)/95	37.10 (36.83, 38.08)/13	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/8	19.00 (18.00, 20.00)/8	22.00 (20.00, 26.00)/0	<0.001***
Investigation				
NLR >3.13 cells/μL	39 (34.5%)/115	19 (27.1%)/111	20 (46.5%)/4	0.035
CRP >5 mg/dL	26 (24.1%)/120	7 (10.9%)/117	19 (43.2%)/3	<0.001***
Chest radiography: total zone involvement‡	1.50 (0.00, 3.00)/166	0.00 (0.00, 1.00)/155	2.00 (1.00, 4.00)/11	<0.001***
MEWS score	0.00 (0.00, 2.00)/8	0.00 (0.00, 1.00)/8	3.00 (2.00, 5.00)/0	
MEWS >3	38 (16.7%)/1	4 (2.2%)/0	34 (72.3%)/1	<0.001***

*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

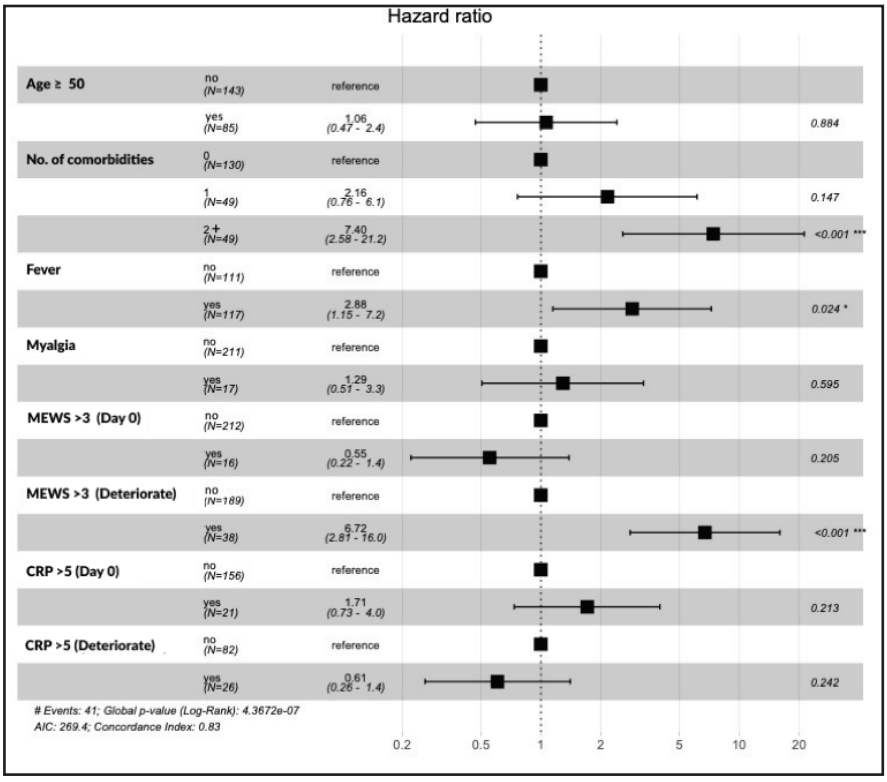

Fig. 1: Forest plot of the hazard ratio for the predictors associated with deterioration of COVID-19 patients.

stable and deteriorated group. Time specified data point analysed at 48 hours, 24 hours before and on the day of deterioration, or day 10 of illness for stable patients. The Kaplan–Meier survival curves were plotted with the purpose of comparing variables, which can be found at Appendix 1. Cox regression model was done for hazard ratio of different risk factors. The two-sided statistical significance level, P-value, was set at 0.05 for all analyses in this study. All were performed using R version 3.6.3.

RESULTS

Table I shows that out of the 228 patients initially admitted with mild illness, 47 had progressed into severe pneumonia requiring oxygen. Overall, 37.3% of patients was ≥50 years old (median age = 42.5, IQR = 28.8–57.0) with more than half of deteriorated patients were ≥50 years old. The median day of illness at time of admission was six days (IQR= 4–8), whereas the median day at deterioration was at day 10 of illness (IQR = 8–12). The median time from admission to deterioration was three days (IQR= 2–5).

For the deteriorated group, 66% had ≥1 comorbidities compared to only 37% in the stable group. On admission, the majority of the deteriorated group ($p < 0.001$) had a fever. Symptoms such as shortness of breath and myalgia were also recorded with significant differences between the two groups, with 19% of deteriorating patients exhibiting these symptoms.

Higher temperature (37.3, IQR = 36.8–38.0), MEWS score >3 (9, 19.1%), neutrophil-to-lymphocyte ratio (NLR) >3.13 (18, 38.3%), C-reactive protein (CRP) >5mg/dL (12, 27.3%), and multiple zone involvement on the chest radiography on admission (2, IQR= 1–3) were significantly different between the two groups.

In the days leading up to outcome, the deteriorated group had higher temperatures and higher respiratory rate, with more than one zone of lung field involvement, as indicated in Tables II–IV. When compared the groups, CRP >5 was significantly different at 24 hours and on the day of deterioration.

As evident from Figure 1, ≥2 comorbidities, presence of fever on admission, and MEWS score >3 (HR of 6.72 ,95% CI: 2.81–16.0, $p < 0.001$). were associated with patients' deterioration. Multiple comorbidities (HR = 7.40, 95%: CI 2.58–21.2, $p < 0.001$) and the presence of persistent fever was associated with progression to severe COVID-19 (HR = 2.88, 95% CI: 1.15–7.2, $p = 0.024$).

DISCUSSION

The COVID-19 pandemic in Malaysia is currently seeing its largest yet challenging wave of infections., The pandemic has imposed a strain in the major designated hospitals and led to the opening of low-risk treatment centres especially in areas of high surges such as cities and the rural areas of the east coast. Front liners and healthcare workers from various levels of training and background have been mobilised to assist in the clinical care and management of these patients in the low-risk treatment centres, while the sicker patients were hospitalised in the designated hospitals for more intensive monitoring. Sim et al. reported that up to 92% were admitted with mild disease and the overall mortality rates in Malaysia were low (1.2%), which is somewhat similar to other reports. However, in low-risk treatment centres where monitoring may not be as intensive as the hospital settings, identification of warning signs and patients who are at higher risk of further deterioration will improve the efficiency of the health system.

We identified patients greater than 50 years old and those with two or more comorbidities as having a higher risk of deterioration. A previous nationwide report[15] showed that having a history of chronic kidney disease and chronic pulmonary disease had the highest risk of developing severe disease. A closer look at the analysis indicates that patients with most chronic conditions, including obesity, were at risk of severe disease. Globally, various reports highlighted a clear and strong age-related gradient of 50–60 years of age and the presence of comorbidities as risk factors of mortality associated with COVID-19. It is not fully known why the presence of advanced age and comorbidities are important risk factors for severe covid infection. Several theories have been postulated such as a disturbed metabolism with high levels of insulin circulating, prothrombotic tendencies due to drugs or even predisposing medical conditions, increased circulating cytokine response, dysregulated gut microbiome, and a defective macrophage-neutrophil function. Studies have shown that age alone is the most significant risk factor for severe disease, and generally, this has also been documented with other coronaviruses and influenza viruses that affect the elderly. A declining immune function or immune senescence and a reduced cell-mediated immunity together with the increased likelihood that an elderly person will have one or more comorbidities that itself can lead to the risk of severe illness.

Chang et al. showed that fever > 37.5°C and chest X-ray (CXR) on arrival were risk factors in predicting progression of COVID-19. Sim et al.[19] showed that the presence of fever of ≥ 37.5°C, diarrhoea, tachypnoea with RR ≥ 21, and an abnormal CXR on presentation were significant risk factors associated with COVID-19 severity. Deborah et al. also showed that persistent prolonged fever beyond seven days from disease onset had a higher risk of ICU admission (11.1% vs. 0.9; $p=0.05$). Additionally, in our study, we showed that symptoms of fever, shortness of breath, myalgia, increased respiratory rate, and increased infiltrates on the CXR were significantly more common in the group that deteriorated.

MEWS is widely used to identify patients at risk of deterioration by triggering an escalated response in an overwhelmed clinical environment. Sylvian et al. studied whether the use of a modified version of the Early Warning Scoring (EWS) could contribute to an early pick up of patients who require ICU admissions. They looked at 36 patients in a 12-hour interval over 36-hour time period and showed median EWS was higher in the group that required ICU care ($p<0.001$). Anna et al. showed that, in the 68 patients who

were retrospectively reviewed, national early warning signs were a good predictor of ICU admission. In their multivariate analysis, MEWS threshold of 5–7 was significantly related to ICU admissions. In our study, we similarly looked at MEWS on admission and at 6-hour intervals till the desired outcome. Additionally, we also evaluated a MEWS threshold of more than 3 predicting deterioration. A lower MEWS score chosen as our aim was to pick up patients who are more likely to require oxygen rather than ICU admission, thus triggering an increased monitoring and clinical review. In the group of patients who deteriorated in our study, the MEWS score was considerably greater on the days of presentation and outcome compared to the stable group. However, a major limitation to MEWS scoring was the accuracy of respiratory rate being estimated. It was done manually and extremely operator dependent and thus may influence the outcome of the study.

Beyond demographics and clinical characteristics, a clear and strong correlation between laboratory parameters such as CRP, neutrophilia, lymphopenia, and elevated levels of D-dimer were often observed in patients who deteriorated or required ICU care. In our study, both CRP and NLR were significant predictors of deterioration. The other laboratory parameters such as ferritin, D-dimer levels were not analysed as there were missing data in some patients. We strongly recommend tracking the rate of change of CRP rather than a single value and correlate it with NLR values to predict patients who are likely to progress. CRP can be a useful surrogate marker of increased Interleukin-6 activity and other relevant cytokine mediated hyperinflammation pathways, which have been implicated in COVID-19 severe lung damage.

The study answers a very relevant clinical question and involves multiple treatment sites, and thus, the findings of this study can be generalised to all treatment sites. However, the study does have several limitations. First and foremost was the retrospective nature of the study. The documentation was based on manual and electronic records and thus may not be accurate/complete. Second, we did not have standardised laboratory investigations in all the three sites, and this led to selective analysis and missing data.

CONCLUSION

We found that in patients presenting with mild illness, factors such as age greater than 50 years, presence of more than two comorbidities, fever, shortness of breath, increased CXR infiltrates, a raised MEWS score of more than 3, CRP values more than 5 mg/dL, and NLR > 3.13 were significantly associated with progress to more severe disease. Thus, in patients who present with the above risk factors, close monitoring in a high-risk centre is recommended with more frequent reviews and escalating treatment where necessary. However, future research is still needed to determine the factors that cause individuals to deteriorate but do not mount a hyperinflammatory response.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR 20-1237-55360).

CONFLICT OF INTEREST

The authors state that there is no conflict of interest to declare.

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ORIGINAL ARTICLE

Expression of fibronection and fibroblast growth factor in rats cutaneous wound given green coffee bean extract

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ABSTRACT

Background: The application of green coffee bean extract is known to accelerate cutaneous wound healing. Fibronectin and fibroblast growth factors (FGFs) are essential in the wound healing process. However, data on the effect of the green coffee bean extract on fibronectin and FGFs are still limited. Objective: This study aimed to determine the effect of the green coffee extract on the expression of fibronectin dan FGFs in rats' cutaneous wounds.

Materials and Methods: Forty male Sprague Dawney rats, aged 2–3 months, weighing 150–200 grams, were randomly divided into four groups. Cutaneous wounds were made 1.5 cm in diameter and under lidocaine anaesthesia. Group I without treatment was the control group, group II was given a green coffee extract dose of 15%, group III was given a green coffee extract dose of 30%, and group IV was given a green coffee extract dose of 100%. The treatment was applied every day without wound debridement. In each group, five rats were sacrificed after 7 days of treatment (proliferative phase), and the rest were sacrificed after 16 days of treatment (remodelling phase). An anatomical pathologist carried out the immunohistochemical examination to assess fibronectin and FGF expression using a blind method.

Results: The expressions of fibronectin and FGF in the treatment groups were slightly higher than those in the control group, both in the proliferative and remodelling phases. Only, fibronectin expression of the green coffee dose of 100% was significantly higher than the control group in the remodelling phase.

Conclusion: The application of green coffee bean extract in cutaneous wounds could increase fibronectin expression.

KEYWORDS:
fibroblast growth factor, fibronectin, green coffee bean extract, FGF, wound healing

INTRODUCTION

A surgical dressing is a vital step in the post-operative care of surgery patients, including in orthopaedic surgery. As orthopaedic wounds are inherently complex, it is imperative that surgical dressing fulfil the needs of wound care management and accelerate wound healing. Some surgical dressings have been used in orthopaedic surgery, such as antimicrobial dressings, silver, zinc oxide, titanium oxide, and iodine. However, there are reports of bacterial resistance to antimicrobial dressings or other surgical dressings, which increase the risk of wound infection and slow wound healing.[1] Therefore, an alternative wound dressing is needed. One of the traditional treatments for open wounds is applying coffee grounds.[2,3] Coffee beans contain antioxidants, such as phenolic acid, polyphenol, and chlorogenic acid.[4] In a previous study, green coffee bean extract (Coffea canephora) could increase wound contraction and the number of fibroblast and blood vessels.[5,6]

Wound healing is a complex and dynamic process that involves the interaction of various cells and molecules. Given that fibronectin, an adhesive molecule, plays an essential role in wound healing, it mediates various cellular interactions with the extracellular matrix.[7] Fibronectin facilitates fibroblast and other cells migration from periwound to the wound bed and epithelial cells over the new basement membrane. A study has shown that applying fibronectin on rats' wounds effectively speeds healing.[8] Fibronectin creates scaffolding that facilitates the fibrogenesis of collagen. The fibronectin cross-links the collagen fibre and contributes to matrix stability. Fibronectin also serves as the anchor points for myofibroblast involved in wound contraction. In normal wound healing, fibronectin plays a role in all phases of wound healing.[9] Another essential molecule in wound healing is fibroblast growth factor (FGF). FGFs stimulate migration and proliferation of fibroblast to wound area. Fibroblast begins to proliferate and produce fibronectin along with collagen.[10]

However, the effect of green coffee bean extract on the expression of fibronectin and FGF of cutaneous wound healing has not been determined. Therefore, this study aimed to assess the effect of green coffee bean extract on the expression of fibronectin and FGFs on the proliferative and remodelling phase of the extracellular matrix in cutaneous wound healing.

MATERIALS AND METHODS

Extraction and preparation of ointment

This study used green Robusta coffee beans Coffea canephora Pierre ex A. Froehner, as identified by the Biotechnology and Engineering Laboratory, University of Jambi. The beans were dried in an oven at 40°C for 24 hours and then crushed using a blender. The maceration extraction method was done using

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70% ethanol as a solvent with a ratio of 1:3, 500 grams of coffee bean powder, and 1500 mL of 70% ethanol. The solution was macerated for 24 hours and stirred occasionally. The solution was filtered using Whatman paper size 41 to get the filtrate, which was then concentrated with a rotary evaporator. Vaseline was used as a base for making 15% and 30% ointment of green coffee extract. The 15% ointment was made by mixing 15 grams of extract homogeneously with Vaseline up to 100 grams, the 30% ointment was made by mixing 30 grams of extract homogeneously with Vaseline up to 100 grams, and the 100% ointment was the extract without Vaseline addition. The ointment manufacture was started by completely melting the Vaseline and adding a certain extract weight as mentioned above.

Wounding model

This study has been approved by the Ethics Committee of Medical and Health Science Faculty, University of Jambi, under the ethical clearance number 713/UN21.6/LT/2018. This study used healthy male Sprague Dawley strain rats, aged 2–3 months, weighing 150–200 grams. The fur on each left back of the rat was shaven, and a full-thickness incision was made with a diameter of 1.5 cm using a scalpel and scissors under subcutaneous anaesthesia using lidocaine around the incision area. The topical ointment was immediately applied to the wound according to the treatment of each group. A total of 10 rats were used for each group. In group I as control, no dressing was applied to the wound. Group II was given ointment of green coffee extract 15%, group III was given ointment of green coffee extract 30%, and group IV was given green coffee extract 100% on the wound. The wounds were left open during the experiment. The treatments were held once a day without wound debridement. However, every time the extract would be applied, the wound was carefully cleaned from the remaining ointment previously given without disturbing the wound. All rats were housed in plastic cages containing two rats each at room temperature (25°C) and 50–80% humidity with a 12-hour cycle variation between light and dark. All rats were given a standard diet and water ad libitum.

Wound contraction

Wound areas were measured daily by tracing the wound area using transparent graph paper and determining its size. The evaluated wound surfaces were used to calculate the percentage of wound contraction by taking the initial size of the wound as 100%. Percentage wound retraction was determined by an equation, (wound area on day 0 – wound area on Nth day)/(wound area on day 0) × 100%.[11]

Sample preparation

Five rats from each group were sacrificed using anaesthesia on the 7th day (proliferation phase) and the 16th day (remodelling phase). Wounded skin samples were taken. Samples were collected in formalin fixative, embedded in paraffin, and cut into free-floating sections of 10 to 15 µm thickness. Paraffin sections were deparaffinised, rehydrated, and then placed in 0.1 M phosphate-buffered saline (PBS, pH 7.4) containing 0.3% Triton X-100.

Antibodies

Anti-Fibronectin (Medaysis, F14) was used as the primary antibody for fibronectin and anti-FGF2/BFGF (Medaysis, C2) as the primary antibody for FGF.

Immunohistochemical procedures

Immunohistochemical staining was manually done to determine selected biomarker expression in the stroma using DAB horseradish chromogen. Thick sections (4 µm) were placed on a positively charged slide and heated at 60°C for 30 minutes. Deparaffinisation in xylene and rehydration was done using alcohol and followed by treatment by administering antigens for 40 minutes at 98°C. The sections were then cooled at room temperature and incubated with a blocking agent, hydrogen peroxide, for 10 minutes, followed by primary antibody incubation for 30–60 minutes. The immunolabelling assessment was carried out by one anatomical pathologist using a blind method. Fibronectin and FGF stainings were interpreted as positive when extracellular matrix, cytoplasm, or membrane staining were detected. Positive cells were evaluated in 10 high-power (40x) for each histology section and counted as positive cell percentage. The scoring was as follows: negative or clear immunoexpression = 0–25% positive cells, weak immunoexpression = 26–50% positive cells, strong immunoexpression = >50% positive cells. Positive control of fibronectin was the placenta, and for FGF2 was the brain.

Statistical analysis

Statistical analysis for each parameter was described as the mean value ± standard deviation (SD). The parametric data were analysed using one-way ANOVA and continued with the Least Significant Difference (LSD) test. The non-parametric data were analysed by the Kruskal Wallis test and continued with the Mann Whitney test. The significance level was set at $p < 0.05$.

RESULTS

The group given coffee bean extract 15% had the highest percentage of wound contraction on the 7th day. LSD test analysis showed a significant difference between the groups given coffee extract 15% and coffee extract 30%, also between the groups given coffee extract 15% and coffee extract 100%, but not significant between the groups given coffee extract 15% and the control group. However, the percentage of wound contraction on day 16 in the group without treatment had not reached 100%, because there were wounds not closed completely. Daily observations of wound contraction in each group are shown in Figure 1.

The expressions of fibronectin and FGF in each group on day 7 and day 16 are described in Figure 2.

Table I describes the expressions of fibronectin and FGFs on the 7th day, where the proliferative phase of wound healing took place. Fibronectin expression in the group obtaining coffee extract 15% did not differ from the control group. In contrast, fibronectin expressions in groups receiving coffee extracts 30% and 100% were higher than in the control group. An increased extract concentration did not cause increasing fibronectin expression. FGF expression in the

Table I: Distribution of fibronectin and FGF expressions on cutaneous wound healing on the 7th and 16th days of each group

Group	Day	Fibronectin expression			Mean score ± SD	P-value	FGF expression			Mean score ± SD	P-value
		Weak	Clear	Strong			Weak	Clear	Strong		
Without treatment	7	3 (60%)	2 (40%)	0	1.40 ± 0,54	-	3 (60%)	2 (40%)	0	1.40 ± 0.54	-
	16	3 (60%)	2 (40%)	0	1.40 ± 0.54	-	3 (60%)	2 (40%)	0	1.40 ± 0.54	-
Coffee extract 15%	7	3 (60%)	2 (40%)	0	1.40 ± 0.54	1.000	2 (40%)	3 (60%)	0	1.60 ± 0.54	0.549
	16	1 (40%)	4 (60%)	0	1.80 ± 0.44	0.221	2 (40%)	3 (60%)	0	1.60 ± 0.54	0.549
Coffee extract 30%	7	0	5 (100%)	0	2.00	0.050	0	5 (100%)	0	2.00	0.050
	16	0	5 (100%)	0	2.00	0.050	1 (20%)	2 (40%)	2 (40%)	2.20 ± 0.83	0.118
Coffee extract 100%	7	0	5 (100%)	0	2.00	0.050	0	5 (100%)	0	2.00	0.050
	16	0	2 (40%)	3 (60%)	2.60 ± 0.54	0.020*	1 (20%)`	4 (80%)	0	1.80 ± 0.44	0.221

P-value by the Mann Whitney Test compared to the control group (without treatment); * significant at $p < 0.05$

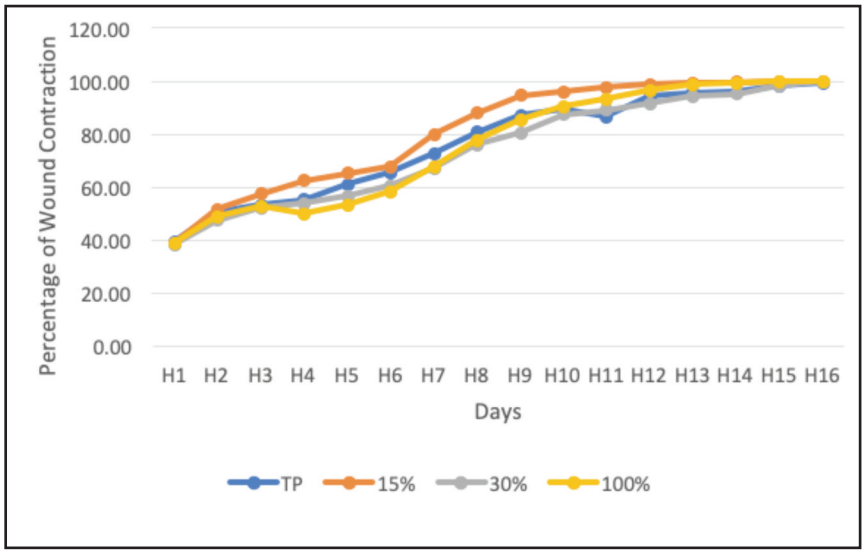


Fig. 1: Mean of wound contraction percentage in each group for 16 days of observation. TP= without treatment.

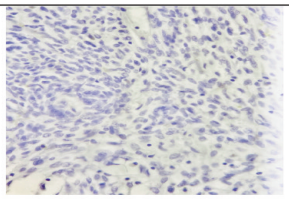
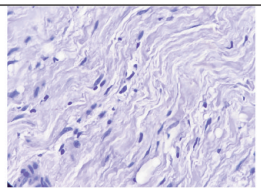
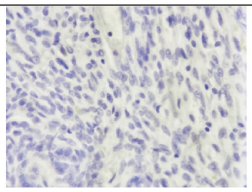
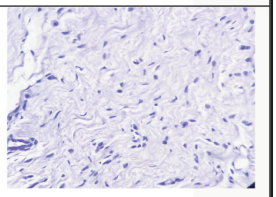
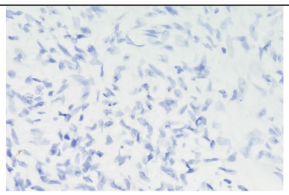
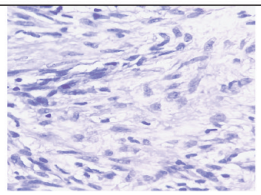
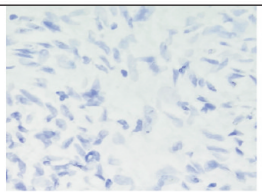
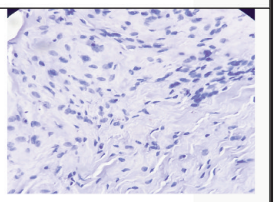
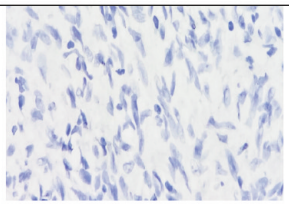
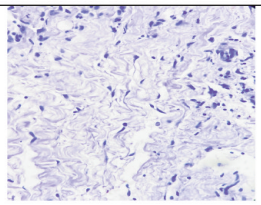
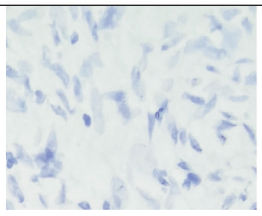
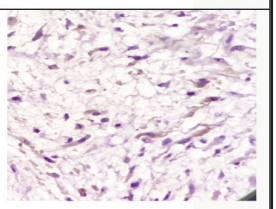
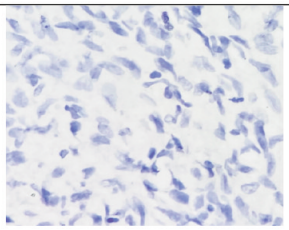
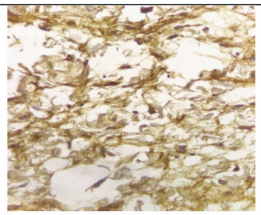
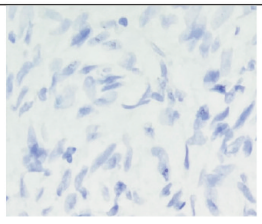
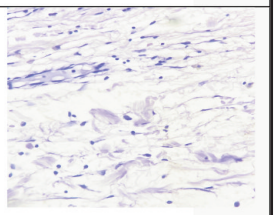
Group	Fibronectin Expression		FGF Expression	
	Day 7	Day 16	Day 7	Day 16
Without treatment				
Coffee extract 15%				
Coffee extract 30%				
Coffee extract 100%				

Fig. 2: Expressions of fibronectin and FGF in each group at day 7 and day 16 with 100x magnification.

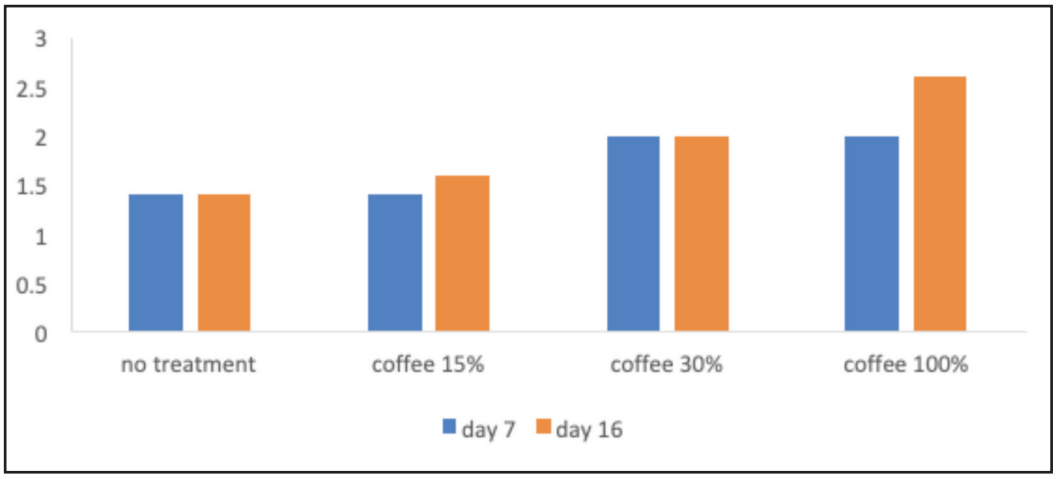


Fig. 3: Mean score of fibronectin expression in each group. Fibronectin expression tends to increase on the 16th day than on the 7th day. On the 16th day in the group obtaining coffee extract 100%, the fibronectin expression was the highest.

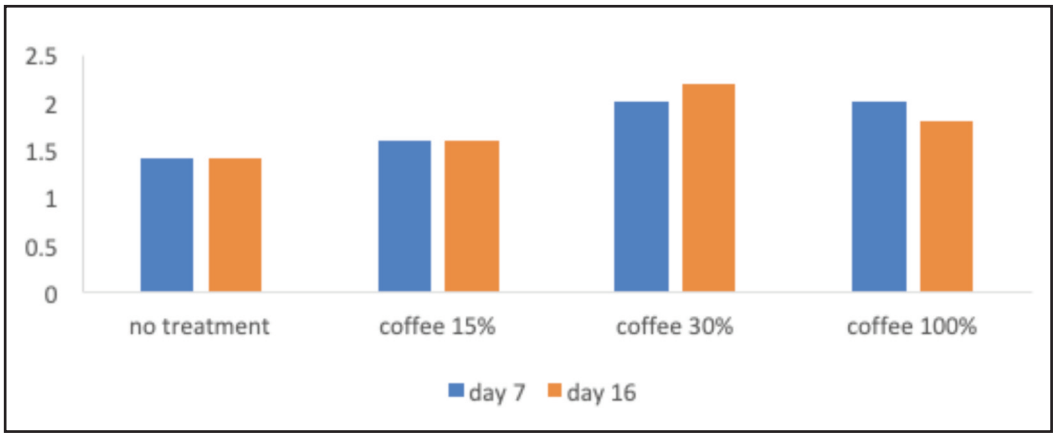


Fig. 4: Mean score of FGF expression in each group. FGF expression tends to be stable on the 16th day compared to the 7th day. There was an increase in FGF expression in the group obtaining coffee extract 30% on the 16th day compared to that on the 7th day, while there was a decrease in the group receiving coffee extract 100%.

treatment group was higher than that in the control group. When the extract was increased from 15% to 30%, FGF expression increased, but when the extract was increased to 100%, FGF expression did not increase. Table 1 also describes fibronectin and FGF expressions on the 16th day, where the remodelling phase of wound healing took place. Fibronectin expression in treatment groups was higher than in the control group. Fibronectin expression in the group given coffee extract 100% was significantly higher than in the control group (Figure 3). FGF expressions in treatment groups were higher than in the control group (Figure 4).

DISCUSSION

Fibronectin emerges in various phases of wound healing. Fibronectin plays an essential role in wound healing, so the lack of fibronectin can cause poor wound healing. Fibronectin is active through all stages of wound healing. In the first phase, plasma fibronectin helps form the clot and assembles an extracellular matrix. Then, platelets help to change plasma fibronectin into fibrillar form.[12] In the inflammatory phase, fibronectin is degraded by proteolytic enzymes and may be oxidatively cross-linked. Fibronectin has a collagen-binding domain that mediates various cellular interactions with the extracellular matrix. However, the synthesis of new fibronectin is activated at the bottom of the wound. The fibronectin serves as an attachment site for the movement of fibroblast and epithelial cells. Fibronectin also serves as the anchor points for myofibroblast involved in wound contraction. The fibronectin cross-links the collagen fibre and contributes to the stability of the matrix.[12,13] Applying fibronectin on the wound of rats effectively speeds the healing.[8] Fibronectin matrix deposition in wound stimulates collagen deposition and contributes to wound contraction. During the proliferation phase, fibronectin is associated with the type III collagen matrix, but collagen type III is then remodelled into type I collagen. Fibronectin creates scaffolding that facilitates the fibrogenesis of collagen.[14] Cellular fibronectin expression in skin wound is induced by TGF-β (transforming growth factor β) and is mediated by CCN2 (cellular communication network factor 2).[12] Fibronectin can bind to many growth factors, such as

TGF β, PDGF, VEGF, and FGF. Therefore, fibronectin can act as a reservoir for growth factors.[15,16] Fibronectin also regulates the lysyl oxidase (LOX), a proteolytic enzyme responsible for covalent cross-linking of collagen fibrils into mature collagen.[10] However, excessive fibronectin can cause abnormal wound healing.[12] In the remodelling phase, the fibronectin matrix will be turned by a disintegrin and metalloproteinase (MMP).[17] Matrix remodelling at the wound depends on MMP and MMP inhibitors. Fibronectin binding to integrin will mediate re-epithelialisation of the keratinocytes.[12]

FGFs have a role in cell migration for tissue formation during wound healing. FGFs play essential roles in the migration of cells since FGFs stimulate the proliferation of fibroblast and angiogenesis. Fibroblast expresses a dermatan sulphate. It seems that FGFs bind to an iduronic acid part of dermatan sulphate.[10] FGF1 and FGF2, which are the subtypes of FGFs, are known to be highly released by damaged endothelial cells and macrophages at wound sites. Syndecans are heparin sulphate proteoglycans in the cell membrane that acts as a cofactor for FGF2 to bind their receptors. Heparin sulphate also protects FGFs from proteolysis, prolonging FGF activity.[16] Dermatan sulphate is responsible for mediating FGF responsiveness in the fibroblast.[10] CCN2 that is upregulated during tissue injury increases fibroblast expression of collagen, MMP, and FGFs.[10] FGF7 and FGF10 play a role in stimulating the migration and proliferation of keratinocytes.[18] Applying FGF2 and FGF10 on a wound could accelerate wound healing.[19]

Continuous applications of green coffee bean extract doses of 30% and 100% in this study could increase the expression of fibronectin on the 7th day; and on the 16th day, the fibronectin expressions on groups treated with green coffee bean extract dose of 100% were significantly higher than the control group ($p < 0.05$). It appears that components in green coffee beans extract could increase wound healing by upregulating fibronectin expression. Two possibilities can occur, either increased synthesis stimulation by TGF-β or inhibition of MMP activity. Study of chlorogenic acid, one of the major components in coffee beans, indicated that chlorogenic acid increased the expression of MMP in bone cells.[20] However, fibronectin degradation can last up to day 21.[14] The effect of green coffee bean extract on FGF expression was not statistically different compared to the control group on the 7th and 16th days. FGF is a paracrine growth factor secreted highly by damaged endothelial cells and macrophages at wound sites, and FGF has a short life.[18]

Vaseline was used for composing 15% and 30% extract concentrations because Vaseline is one of the safe and cost-effective moisturizers. The selection of a semisolid base influences the transdermal delivery of active substances.[21,22] The differences in the effect of each dose of green coffee bean extract were probably due to the delivery factor of the active compound throughout the Vaseline into the wound area. Percentages of wound contraction in the treatment groups were higher than in the control group. The limitation of this study was that the number of samples was small.

CONCLUSION

Coffee beans are used as a traditional wound medicine. Fibronectin and FGF are two important components in the wound healing process. Here, we assessed the effect of green coffee beans in vaseline base on the expression of these two components in cutaneous wounds by immunohistochemistry. This research concludes that the application of green coffee bean extract to cutaneous wounds could modulate fibronectin expressions.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST DECLARATION

The authors state that there is no conflict of interest to declare.

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A cluster randomised controlled trial on effectiveness of health education-based intervention to improve parental practice in preventing unintentional childhood injury among parents attending health clinics: A study protocol

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ABSTRACT

Introduction: Unintentional childhood injuries is one of the public health challenges among developing countries. The injuries often cause mortality and have significant burden of morbidity in Malaysia, and this can be prevented. Parents play important role in practicing preventive measures to reduce likelihood of unintentional injuries among their children. The objective of the study is to develop, implement, and evaluate the effects of health education intervention on parental practices to reduce unintentional childhood injuries among parents of young children.

Materials and Methods: Health education module focusing on preventing childhood unintentional injuries was developed based on information–motivation–behavioural skills (IMB) theory. This intervention was implemented among parents of children under seven years attending government health clinics in Putrajaya. The effectiveness of the intervention was assessed using single-blinded, randomised controlled trial. Parents were excluded if their children have any chronic disease or disabilities or are currently participating in any other community trials. All four health clinics in Putrajaya with eight personalised care zones/groups were included in the study and randomly assigned to either intervention or control groups after the recruitment of eligible parents is completed. The intervention was delivered by the researcher, and data consisting of validated self-administered parental questionnaires were collected at the baseline, one-month post-intervention and three-month post-intervention to assess the effects of the intervention. Data were analysed using Generalised Linear Mixed Model (GLMM) adjusting for covariates.

Results: The study is anticipated to be able to discover factors associated with injury preventive practice among the parents of children attending selected government child health clinics in Putrajaya and determine the effect of the health education intervention on the parental injury preventive practice.

Conclusion: The implementation of the intervention to the parents is expected to improve the parents' knowledge, motivation and practice to prevent unintentional childhood injuries. The health education module developed in this study can be taught to the health staff to standardize their knowledge and transfer of information to the parents during visit. The intervention module can be used to complement existing health education activities in the government health clinics.

KEYWORDS:
information-motivation-behavioural skills model, theory–based health education, child injury prevention, parental injury preventive practice

INTRODUCTION

Childhood injury is now a growing global public health concern as it carries a significant burden with wide range of personal, social, and economic implications. Injury-related causes are one of the major causes of death among children under 14 years worldwide and also the leading cause of death and long-term morbidity among children under five years in the last decade.[1] From all injury-related deaths, unintentional injuries accounted for more than 90% of these deaths, and this is alarming as unintentional injuries are preventable when all the appropriate safety measures are taken. Young children are exceptionally vulnerable to unintentional injuries because of their nature of curiosity to explore the environment; yet they are not capable of protecting themselves or understand the consequences and danger of their behaviour.

The WHO Global Burden of Disease reported that the global reduction in disease burden from infectious and nutritional causes were accompanied by significant increase in the injuries and non-communicable disease burden.[2] The ranking of injuries as the cause of death among children has increased over the years consistently with age and increasing sociodemographic index. Road traffic injuries were at the top, followed closely by drowning. The burden of childhood injury is the heaviest among the children in poor countries with poor incomes, and within these countries, the burden is greatest among the family with low-socioeconomic status.[3] In Malaysia, a nationwide population survey reported the prevalence of injury among 116,600 children under seven years in Malaysia in 2011 was 8.3% (95% CI: 6.4–10.4).[4] The latest population survey in 2016 only captured the prevalence of unintentional injury among 76,920 children

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aged one to four years, which is 3.8% (95% CI: 2.8–5.2), and it is difficult to comment on the trend, but it remains prevalent in the community.[5] Not only the child can be severely disabled, but injuries also impacted the caregivers and the family members in term of economic costs of treatment and medical care, psychological wellbeing as well as their productivities in general. The overall economic cost of childhood injuries was estimated to be between USD0.5 million and USD9.5 million per year.[6]

Sustainable Development Goals (SDGs) call for concentrated effort to ensure better health of the children by ending preventable deaths for children under five years and reducing the number of deaths from traffic injuries for older children (5–18 years old) under the health targets.[7] Therefore, countries are now looking at reducing the burden of childhood injury as the main agenda to improve child health as the burden has shifted away from the communicable diseases that are caused by sanitation and hygiene factors. Prevention and control of unintentional injuries in childhood age often use a combination of passive and active strategies where the passive strategies are referring to the environmental and products' change, and active strategies are directed towards behavioural changes.[8] Parents and caregivers play a vital role in adopting appropriate injury preventive behaviour to help prevent the unintentional injuries among the children and subsequently reducing the risk of any injuries.

Parental factors are one of the important protective factors in reducing the overall risk of injury in children. Injury risk can be defined as any factors or in combinations of individual, familial, social, economic, and physical environment that can contribute to the occurrence of injury event.[9] There is no universal definition on injury preventive practice or a standard checklist of what constitutes good practice. Each type of injuries has its own practice based on different circumstances and background. However, parental injury preventive practices can be broadly grouped under three strategies: teaching own children safety measures,[10] safety proofing behaviour,[11,12] and parental supervision.[13-17] These three measures were used in combination for this study as they cover all parental practices on preventing unintentional childhood injuries.

Factors associated with childhood injury preventive practice tend to be multifactorial, which include parental and child factors and socioeconomic and environmental factors. The modifiable factors were largely the parental factors such as knowledge,[18-20] motivation,[21-24] and behavioural skills.[25,26] These modifiable factors are amenable to health intervention if designed properly, thus improving the parental preventive practice and ultimately reducing the risk of childhood injury. These factors are consistent with the construct of information–motivation–behavioural skills (IMB) theory where it illustrates the significance of information (knowledge) and motivation, as well as self-efficacy to ensure successful behaviour change. Although the combination and synergistic effect of all the contributing factors to childhood injuries are very complex and difficult to pinpoint the exact occurrence of injury, evidence however has shown that modification of any determinants is sufficient to reduce the overall risk of injury.[27]

At present, there are initiatives to address injury prevention among children in Malaysia, but they are still lacking compared to other developed countries. Current injury prevention programs scatter across ministries and non-governmental organisations throughout the country. National child health program delivered through primary health clinics in Malaysia uses the child health record book as a tool to educate parents regarding child safety and basic injury prevention measures, but the content and the effectiveness of the intervention have never been evaluated. Furthermore, other injury prevention approaches, such as enforcement and adherence to law, remain difficult if the behaviour is not changed. Evidence suggests that health education alone can achieve the most modest gain but legislation alone without education component will result in non-compliance and objective will not be met.[28] This emphasises on the importance of health education as main strategy in preventing childhood injuries. Literature on risk factors and predictors of childhood injury is quite prevalent and able to provide rich body of knowledge to the policymakers and healthcare providers; however, the evidence on the effectiveness of intervention is still scarce. A review of study designs in published literature related to the prevention of unintentional childhood injury between 2013 and 2016 found that majority of the studies are descriptive or observational with only 3% of the studies being randomised controlled trials.[29] This highlights the gap of knowledge in knowing which intervention is effective to improve the childhood injury preventive practice and reduce the risk of childhood injury.

The objective of the study is to develop, implement, and evaluate the effects of IMB-based health education intervention on parental practices to reduce unintentional childhood injuries among parents of young children.

MATERIALS AND METHODS

Study location

The study was conducted in four government primary health clinics in Putrajaya, Malaysia. Putrajaya represents the urban state in Malaysia as the urbanisation level is 100% as reported by the Department of Statistics Malaysia. This justifies the location chosen for the study as the National Health Morbidity Survey 2011 and 2016 reported that the prevalence of childhood injury is significantly higher among the urban population. The services provided in the primary health clinics include well-child clinic where it caters for all children aged below seven years who come regularly for immunisation, growth and developmental assessment, and monitoring of physical or any learning disorder. Each clinic has personalised care zones where the families were grouped based on their residential address and being taken care of by the same team of health personnel throughout any visit at the clinic. The groups were given different appointment dates according to the schedule in each clinic. There are a total of eight personalised care zones within four health clinics in Putrajaya.

Study design

This study is a cluster, randomised, single blinded, controlled trial with two parallel arms of intervention and wait-list control groups. The protocol for this study has been reported

according to the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) 2013 Guidelines.[30]

Study duration

This study took about 24 months to complete – from the proposal of the study, the development and validation of the questionnaire, development, validation, and testing of the implementation of the health education intervention program, and lastly the implementation and evaluation of the intervention programme. The activities of the intervention program commenced in April 2021. Figure 1 shows the flowchart of the study based on CONSORT extension for cluster trial 2012.[31]

RESULTS

Study population and study setting

The study population for this study was one of the parents of children under seven years (0 to 6 years old) who are registered at the primary health clinics in Putrajaya and attending the follow-up. Inclusion criteria are parents aged 18 years and those who are literate and able to communicate in Malay or English language. Exclusion criteria are parents with index child having chronic diseases or disabilities or currently participating in other community trials. Parents who score extremely low in the baseline survey were also excluded from the study to allow for immediate intervention with regards to child safety. The baseline survey is the same set of questionnaires, which was used throughout the study.

Sample size

The sample size for this study was calculated using formula for mean differences within the intervention groups at baseline and three months post-intervention. The sample size was inflated by the design effect for fixed size cluster study design,[32] with 95% level of significance, 80% power, and 20% attrition rate. Based on the previous study on the effectiveness of injury prevention intervention,[33] their intra-cluster correlation coefficient of 0.05 was used; thus, the total number of participants required in this study was 178 with equal number in each control and intervention groups.

Recruitment

Participants were recruited directly from the health clinics. Standing banner and poster were placed strategically within the clinic waiting area two months before the commencement of the study. Health clinic staff helped to identify suitable participants and distribute study flyers directly. The benefits of the study include improving knowledge and skills on how to prevent unintentional childhood injuries, and this information was conveyed in the flyers and banners to convince parents to participate in the study and adhere to the study protocol. All parents who agreed to participate scanned the QR code that will register their details and consent, as well as screening questions to assess their eligibility to participate.

Randomisation, allocation concealment, and blinding

The randomisation was conducted at the cluster level, where the randomisation units were the personalised care zones. Respondents in each personalised care zone were allocated to either control or intervention group based on the cluster randomisation results. By confining the intervention and control to specific personalised care zones, contamination issues can be avoided since they are segregated by residential address, health personnel team, and appointment date, thus increasing the validity of the study. The randomisation was made through a computerised sequence generation created by computer software from the website, www.random.org.[34] Block randomisation was used in this study to preserve the balance between the number of intervention and control groups. Randomisation process was conducted by an independent person who is not involved in this study. The person generated the random allocation sequence, enrolled the clusters, and assigned the clusters to either intervention or control group in strictest confidential manner. Single blinding technique was used where participating respondents were not aware of the status of the group participation. The researcher allocated the group to interventions based on the randomisation result provided by the independent person.

Intervention

Intervention development and validation

The intervention module is named 'Keeping Kids Safe', which aims to improve parental injury preventive practice, subsequently reducing the risk of unintentional childhood injuries. The intervention module was newly developed by the researcher based on extensive literature review including peer-reviewed journal articles and established guidelines for childhood injury prevention. The components of IMB theory were used to design the intervention program. It consists of three constructs: information, motivation, and behavioural skill. The details of the intervention module content and delivery are summarised in Table I. The module has been reviewed for their contents by Family Medicine Physicians who work in primary care clinics, Public Health Physicians from the health ministry and state health department, senior health educator officer, and academician. The module was then piloted to a small group of respondents where the presentation and readability of the contents were being appraised. Discussion and feedbacks were considered to make adjustment and modification to further improve and finalise the module.

Intervention format and delivery

The module was developed into a series of health education videos and infographics. There are a total four animation, non-narrated videos of three to five minutes duration each. The first two videos were designed to deliver mainly information regarding risk of injury and child development stages. The third video contained real case scenarios from local news and explanation on the myths and facts related to childhood unintentional injury. This video aimed to increase parents' motivation and self-efficacy in injury prevention. The last video summarised important injury preventive practices. Participants received one video per day for four consecutive days. At two months of interval post-intervention, participants were sent with infographics that summarise the content of video they receive during the intervention week as reminder. All the content of the intervention module was delivered online via individual WhatsApp to each participant in the intervention group.

Control group

The control group continued their usual care and received existing health education from the clinic delivered by their

Table I: Summary of intervention program content and delivery

Intervention program	IMB constructs*	Content	Format and delivery	Week
Baseline survey	-	Questionnaire	Google form link	0
Module 1	I	Introduction to injury Statistics of injury in Malaysia Types and risk of injuries	Video	4
Module 2	I	Child development stages and risk of injury	Video	4
Module 3	M, B	Real cases scenarios from local news Myths and facts	Video	4
Module 4	I, B	Injury preventive practice Self-efficacy	Video	4
Post-intervention survey 1	-	Questionnaire	Google form link	8
Reminder 1	I, B	Childhood injury	Infographic	12
Reminder 2	M	Consolidate appropriate beliefs and attitudes for preventive practice	Infographic	12
Reminder 3	M, B	Self-efficacy	Infographic	12
Reminder 4	I	Injury preventive practice	Infographic	12
Post-intervention survey 2	-	Questionnaire	Google form link	16

* I= Information, M= Motivation, B= Behavioural skill

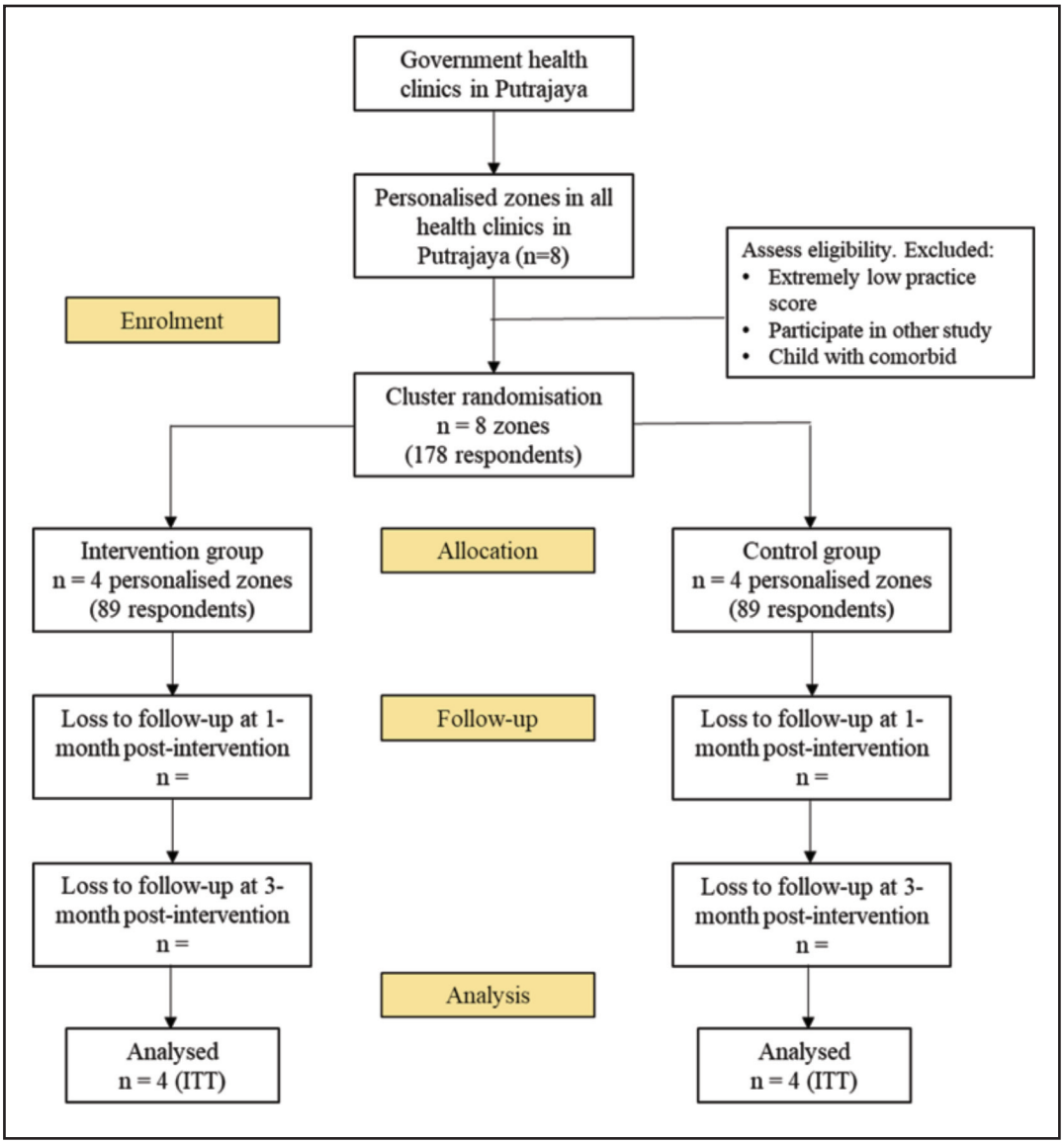

Fig. 1: Flowchart based on CONSORT extension for cluster trial 2012.

personalised health team during their visit to the health clinic. The existing health education is based on child health record book checklist and standard advice based on child's age group. To keep the control group blinded, they were informed that once they participate in the study, health education module will be given at any time within the six months of participation. Participants in the control group received all the health educational videos on completion of data collection (wait-list).

Data collection

In view of various restrictions at health clinics due to COVID-19 pandemic, data collection was conducted online. Each registered participant was assigned a unique code number and link to the online questionnaire via individual WhatsApp. Data were collected at three timepoints: baseline (T0), one month after the intervention (T1), and three months after the intervention (T2). The questionnaires were adapted from existing self-report scales to assess the injury preventive practice and its associated factors, including the sociodemographic background of the participants. To minimise loss in follow-ups in cases where online questionnaire is not feasible, telephone interview was conducted. Reminders were also sent in form of short messaging system (SMS) to prompt participants to answer the questionnaire in a timely manner.

Quality control

The questionnaire has been reliably tested among 30 parents of children under seven years attending government health clinics and analysed by SPSS to compute the Cohen's Kappa and Intraclass Correlation Coefficient value. Internal consistency of the questionnaire was assessed using Cronbach's Alpha test. The findings were used to finalise the questionnaires before administration to actual respondents.

Outcome assessment

The primary outcome measure of the study is the change in parent's preventive practice score, which refers to the total injury preventive practice score. It was calculated based on 30 items in the last section where it consists of three components: teaching own children, safety proofing, and parental supervision. This outcome was compared between the intervention and control group, and within each group at baseline, one-month and three-month post-intervention.

The secondary outcome measure of the study consists of the IMB construct score change, including the knowledge, motivation, and behavioural skills of the parents. Knowledge change refers to changes in total knowledge score as measured in the questionnaire, which assess respondents' level of knowledge in the developmental stage of children and risk factors for unintentional childhood injuries. Motivation change refers to the summation of score calculated in the questionnaire where it consists of attitude, beliefs, and subjective norms of the respondents towards injury preventive practice. Behavioural skills score change refers to self-efficacy components in the questionnaire where the score calculated is based on the five statements. Higher score indicates higher self-efficacy in preventing childhood injuries.

Data analysis

Final data were entered and analysed using the computer software Statistical Package for Social Sciences (SPSS) version 23. No identifying information was recorded, and data were encrypted with password to ensure safety and confidentiality. Prior to the analysis, data were screened for out-of-range values, error, or missing data, and they were handled using multiple imputations. Additionally, sensitivity analysis was conducted in form of intention-to-treat (ITT) principle to ensure robustness and validity of the study outcome. Descriptive statistical analysis was used to describe the sociodemographic characteristics of all the participants, knowledge, motivation, behavioural skills, and injury preventive practice score. Univariate statistical analysis was performed to compare the baseline differences between the intervention and control group. An independent t-test was used to compare the means of two groups in normally distributed continuous variables, while Wilcoxon-Mann-Whitney test was conducted to compare the medians between two groups of non-normally distributed continuous data. For categorical variables, Chi-square and Fisher's Exact tests were used to compare the differences. Generalised Linear Mixed Model (GLMM) analysis was used in this study to determine the effectiveness of the health education intervention on the parent's preventive practice against childhood injury between the intervention and control groups. The results of the analysis are presented as 95% confidence interval, and the level of significance in this study is set at alpha value of 0.05.

DISCUSSION

The study anticipated to be able to determine the effect of the health education intervention on the injury preventive practice. The mean score for preventive practice is expected to be higher immediately after the intervention as compared to the baseline score and to be sustained at three-month follow-up.

The result of this study provides an insight on the effectiveness of theory-based intervention to parents of young children in improving their preventive practices to reduce unintentional childhood injuries. The use of educational video as interventional method can effectively supplement existing health education at the primary care setting and help to sustain parents' motivation and self-efficacy to improve their injury preventive practices.

This is an experimental study where the variables and environment of the intervention conducted are in controlled environment. Therefore, the limitations to this study include caution interpretation of the generalisability of the study findings. Furthermore, cluster randomisation may cause selection bias if randomisation done prior to recruitment of participants as the researcher knows about the allocation. However, this can be minimised by adhering to CONSORT flow whereby the randomisation is done only on completion of participant recruitment. Lastly, the outcome measure is that the parental preventive practice, which is self-reported, imposed risk of social desirability or recall bias compared to observed behaviour practice.[35]

In summary, the implementation of the intervention to the parents is expected to improve the parents' knowledge, motivation, and practice to prevent unintentional childhood injuries. The health education module developed in this study can be taught to the health staff to standardise their knowledge and transfer of information to the parents during visit. The intervention module can be used to complement existing health education activities in the government health clinics.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was registered under National Medical Research Registry (NMRR) and approved by the Malaysian Research Ethical Committee board (Reference: NMRR-20-1819-54615, Date: 15/10/2020). This study protocol was also registered with the Thai Clinical Trial Registry with the registration number TCTR20200629002, Date: 15/06/2020. Written informed consent was obtained from respondents before collecting data. All the personal details of the respondents and information gained by the study will be kept confidential and will be used for research purposes only.

CONFLICT OF INTEREST

The authors declare no competing interests.

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ORIGINAL ARTICLE

Problems faced by Malaysians during the Movement Control Order and Conditional Movement Control Order: A cross-sectional study

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ABSTRACT

Introduction: The COVID-19 pandemic had caused Malaysia to introduce a lockdown approach for the first time that was due to an outbreak of infectious disease. This was bound to create certain problems as it disrupts Malaysians' daily routine and way of life.

Materials and Methods: A cross-sectional study to identify the problems faced by Malaysian Social Media Users during the Movement Control Order (MCO) and Conditional Movement Control Order (CMCO) was conducted. An online survey that assessed the knowledge, attitude, and practice of COVID-19 was shared via social media.

Results: The response of the attitude module from the participants during MCO (n=2073) and CMCO (n=2720) were analysed. Chi-squared and Fisher's Exact Test showed that the male, unmarried, young (<40 years old), and employed participants were the most affected (p<0.05) when responding to a list of major problems faced during MCO/CMCO – 'Emotional difficulty being confined', 'Did not get paid due to missing work', 'Unable to communicate with family members who were not there', 'Unable to get food or water', 'Unable to get regular medical care or prescriptions', and 'There were no problems for me during MCO/CMCO'.

Conclusion: The problems that were faced by these groups need to be addressed for better public health interventions and policies to win against the war on the ongoing COVID-19 pandemic.

KEYWORDS:
COVID-19 pandemic, Malaysia, Movement Control Order, social problems

INTRODUCTION

On 11th March, 2020, the World Health Organization (WHO) characterised the COVID-19, caused by the novel strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic.[1] The virus was initially identified in December 2019 in Wuhan, China. Due to its characteristic of being highly and rapidly contagious and high mortality rate among the vulnerable groups, the Chinese government decided to impose a total lockdown on Wuhan on 23rd January 2020.[2] Lockdowns are considered more restrictive non-pharmaceutical interventions (mrNPIs), which included mandatory stay-at-home and business closure orders.[3] The goal was to reduce case fatality rate, infective rate, and health system overload in the absence of pharmaceutical options. This NPI was later quickly adopted by other countries in the world, including Malaysia. According to the Centers for Disease Control (CDC), acknowledging stress symptoms resulting from the lockdowns and the disease itself is vital.[4]

Under the Prevention and Protection of Infectious Disease 1998, the Movement Control Order (MCO) was imposed in Malaysia starting from 18th March, 2020, to curb the spread of the virus in the country.[5] The regulations of the MCO included ban on gathering (religious, sports, recreational, social or cultural), restrictions on movements (except for special purposes or essential activities), travel bans nationwide (except for special purposes or essential activities), and international travel bans (except for returning Malaysians), and all educational institutions and premises (government and private) were closed (except for special purposes or essential activities).[6] The public was asked to work from home and was urged to stay at home to reduce the spread of infection. Multiple roadblocks were set around the country to ensure its effect and allowing only one or two (if reasonably necessary) people to travel for food, daily necessities, and healthcare to only within a radius of not more than ten kilometres from a person's residence.[7]

Due to the decreasing trend in cases, the Conditional Movement Control Order (CMCO) was announced on 1st May, 2020. During CMCO, many sectors of the economy (except entertainment, hospitality venues, schools, and religious gatherings) were allowed to operate under strict standard operating procedures (SOPs).[7]

In Malaysia, both Ministry of Health (MoH) and National Security Council (NSC) played an active role during these periods. SOPs were introduced throughout the MCO and CMCO period for the public to adhere. If a person is convicted for breaching any of the regulations, that person will be liable to a fine of not exceeding RM1,000 or to imprisonment for a term not exceeding 6 months, or to both.[7] Social distancing, wearing of face masks in public places, temperature checks, and scanning the 'MySejahtera' app for contact tracing had become the 'new norm' for Malaysians. Numerous financial aid and stimulus package were offered

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throughout the MCO periods to ease the burden of the public. The publics' cooperation towards the governments order is one of the important ways to overcome the outbreak of COVID-19 pandemic. Adhering to the control measures and keeping ones' self-up to date regarding the knowledge, attitude, and practice are the crucial steps to assure the success.[8]

This was the first time that Malaysia had to introduce a lockdown approach due to an outbreak of infectious disease. In scientific terminology, the word 'Lockdown' means 'Restrictive Mass Quarantine'.[9] The harmful effect of this mrNPI – such as hunger, opioid-related overdoses, missed vaccinations, increase in non-COVID diseases from missed health services, domestic abuse, mental health and suicidality – needs to be addressed.[3] A study on psychological impact of coronavirus on Malaysian university students showed that 87.7% of students were experiencing mild to severe anxiety.[4] Brooks et al.[10] reported that duration of quarantine, fears of infection, frustration and boredom, inadequate supplies, inadequate information, finances, and stigma are stressors during and post-quarantine. In order to improve communication efforts and policies, public health officials and clinicians need to learn more about public concern and problems during this kind of outbreaks.[11]

Currently, there are limited studies on the general problems faced by Malaysians during these restrictions of movements period. With Malaysia being a long middle-income country, Eyawo et al.[12] underlined the risks of lockdown measures, such as starvation, economic ruin, and neglect of other pressing health issues, in low- and middle-income countries (LMIC). The aim of the study was to identify the problems faced by Malaysian social media users during the MCO and CMCO hoping to facilitate improvement for policies and programs in case there are future lockdowns. In view of the movement restriction, it was feasible to conduct an online survey. A survey conducted by Malaysian Communication and Multimedia Commission (MCMC) in 2018 showed that there were about 24.6–27.8 million social media users in Malaysia. Of those, more than 90 % owned a WhatsApp or Facebook account, followed by 50% who has Instagram and 20% who has Twitter or Telegram.[13] With these high numbers of social media users in Malaysia, we believe we were able to paint a representation of the problem via this online survey.

MATERIALS AND METHODS

This study analysed attitude module of an online cross-sectional study performed among social media users in Malaysia using self-administered online questionnaires during MCO (NMRR-20-743-54644) and during CMCO (NMRR-20-1064- 55142). Sample size estimation was calculated using the population portion formulae.[14] Prior data indicate the proportion of Malaysian social media users with good knowledge on COVID-19 was 0.78 and population size was 2270000. If the Type I error probability and the probability and precision were 0.05 and 0.05, respectively, we will need to study 323 samples. With an additional of 20% dropout rate, the sample size was 404 samples. Data collection was done for one week during MCO (17–24 April, 2020) and two weeks during CMCO (5–19 June, 2020). Data collection was made through Google Form and distributed via investigators' social media platforms (including but not limited to Facebook, WhatsApp, Instagram, Twitter, and Telegram). Participants who were Malaysians and above the age of 18 were required to answer two sets of self-administrated questionnaires: a demographic and a knowledge, attitude, and practice on COVID-19 pandemic. Participants were expected to spend 15–20 minutes to complete the questionnaire.

The questionnaire was adopted from a few studies on COVID-19 and other outbreaks with permission for adopting and modifying the questionnaires by the authors.[8,11,15-16] The questions were modified to suit the current situation in Malaysia and pertaining to COVID-19 only. Researchers have decided to maintain the questions in English according to EF English Proficiency Index, which is the world's largest ranking system of countries on English skills, and Malaysia has high English proficiency and is ranked 3 in Asia and 22 out of 100 countries.[17]

The questionnaire was piloted among 10 participants sampled from the target population to troubleshoot on the quality, language barrier, possible difficulties detected during filling, and estimated time required for its completion and subsequently excluded from the data analysis.

Statistical Analysis

Results were analysed using RStudio version 1.2.1335 (RStudio, Inc., Boston, MA, USA). Descriptive statistics were presented as mean and standard deviation (SD) for continuous variables, whereas they were presented as frequency and percentage for categorical variables. Inferential statistics for continuous variables were performed using independent t-test and one-way ANOVA. Inferential statistics for categorical variables were performed using Chi-Square Test and Fisher's Exact Test with $p<0.05$ as statistical significance.

RESULTS

Sociodemographic Characteristics

The socio-demographic of the participants of both studies are presented in Table I. A total of 2163 participants completed the survey during MCO, whereas 2865 participants completed during CMCO. We analysed 2073 and 2720 responds after data cleaning. The mean age of participant was 36.89 years (SD 9.98) and 34.76 years (SD 9.03). During MCO, there were 1508 (73%) female participants, 1282 (62%) were married, and 1913 (92%) were with tertiary education, whereas during CMCO, 1890 (69%) females participated, 1529 (56%) were married, and 2428(91%) had tertiary education. Nearly half of the participants were from central Malaysia (namely Kuala Lumpur, Selangor, and Putrajaya) with 972 (47%) during MCO and 1161 (43%) during CMCO. There were 886 (43%) and 1795 (66%) participants who answered social media as their main source for information on COVID-19.

Interestingly, when asked whether MCO/CMCO a major problem for them, 87% and 79% of the participants claimed that they did not face any major problems, respectively, as

Table I: Sociodemographic characteristic of study participants for knowledge, attitude, and practice (KAP) of social media users in Malaysia during MCO and CMCO

Variables	MCO		CMCO	
	N	Percentage (%)	N	Percentage (%)
Age (years)				
<30	624	30	1004	37
31–40	797	38	1060	39
>40	652	31	656	24
Total	2073	100	2720	100
Sex				
Male	565	27	830	31
Female	1508	73	1890	69
Total	2073	100	2720	100
Marital Status				
Married	1282	62	1529	56
Unmarried	791	38	1191	44
Total	2073	100	2720	100
Education Level				
Primary school	12	1	11	0
Secondary school	118	6	170	6
Tertiary education (Vocational, Diploma, Bachelor Degree or higher)	1913	92	2482	91
Prefer not to say	30	1	57	2
Total	2073	100	2720	100
Profession				
Healthcare	1087	52	451	17
Non-healthcare	986	48	2269	83
Total	2073	100	2720	100
Regions				
Northern	277	13	477	18
Eastern	185	9	291	11
Central	972	47	1161	43
Southern	310	15	449	17
East Malaysia	329	16	342	13
Total	2073	100	2720	100
Source of Information				
Posts and videos on social media	886	43	345	13
Official websites of WHO/CDC/KKM/MKN	661	31	1669	62
Newspaper and television shows (daily news programs, press conference)	388	19	685	25
Consultation with doctors and hospital staff	62	3	6	0
Hospital posters and cut-outs	34	2	0	0
Conversation with family and friends	26	1	8	0
Others (journals, mobile apps, various sources)	16	1	7	0
Total	2073	100	2720	100

Table II: Frequency and percentage of the participants who answered: The MCO/CMCO was a major problem for me

Statement	Yes		No		I do not know	
	n	%	n	%	n	%
The **MCO** was a *major* problem for me.	218	11	1809	87	46	2
The **CMCO** was a *major* problem for me.	457	17	2147	79	116	4

shown in Table II. However, when answering detailed common major problems listed in the questionnaire, only 62% and 35% of the participants answered they have no problems during MCO/CMCO, respectively, as can be seen in Figure 1 and Figure 2.

Results of inferential statistical analysis for categorical variables can be seen in Table III. There we presented categorical variables that had statistical significance ($p<0.05$) that had major problems during the MCO/CMCO, and we bolded the variables that were presented in both studies for comparison.

DISCUSSION

To understand how the lockdown effected these different socio-demographic groups, we analysed and discussed the 6 statements that the participant responded to. In each statement, we provided different literatures to support on possible reasons why the participants felt what they felt during the lockdown.

There were no problems for me during the MCO/CMCO.

Participants aged more than 40 years and married were statistically significant demographic variables for this statement in both MCO and CMCO. This result is in line with the study by Kowal et al.[18], which may be attributed by the

Table III: Statistically significant statements identified major problems faced during MCO/CMCO. Demographic groups that appear in both MCO/CMCO are in bold

There were no problems for me during the MCO			There were no problems for me during the CMCO		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Age			Age		
>40	449(68.9)	<0.001	>40	262(39.9)	0.002
Sex			Marital Status		
Female	977(64.8)	0.0002	Married	594(38.8)	<0.001
Marital Status					
Married	835(65.1)	0.001			
Education					
Tertiary education	1198(62.6)	0.005			
Employment Status					
Yes	1134(63.6)	0.004			
The MCO was a major problem for me			**The CMCO was a major problem for me**		
Variable	**N(%)**	**p value**	**Variable**	**N (%)**	**p value**
Sex			Age		
Male	97(17.2)	<0.001	<30	199(19.8)	<0.001
Marital Status			Sex		
Unmarried	98(12.4)	0.02	Male	201(24.2)	<0.001
Education Level			Marital Status		
Primary-school	14(11.9)	0.03	Unmarried	221(18.6)	<0.001
Source of Information			Education Level		
Newspaper and TV shows (news, press conference)	52(13.4)	0.03	Prefer not to say	10(17.5)	<0.001
			Employment Status		
			No	91(18.3)	0.001
Emotional difficulty being confined			**Emotional difficulty being confined**		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Age			Marital Status		
<30	127(20.4)	<0.001	Unmarried	476(40.0)	<0.001
Marital Status					
Unmarried	152(19.2)	<0.001			
Employment Status					
No	76(26.2)	<0.001			
Profession					
Healthcare	203(18.7)	<0.001			
Region					
Central	168(17.3)	0.04			
Did not get paid due to missing work			**Did not get paid due to missing work**		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Sex			Age		
Male	62(11.0)	<0.001	<30	134(13.3)	<0.001
Profession			Sex		
Healthcare	93(8.6)	<0.001	Male	113(13.6)	<0.001
			Education Level		
			Secondary school	34(20.0)	<0.001
			Profession		
			Non-healthcare	258(11.4)	<0.001
Unable to communicate with family members who were not there			**Unable to communicate with family members who were not there**		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Education Level			Marital Status		
Secondary school	19(16.1)	<0.001	Married	281(18.4)	0.01
Employment Status			Education Level		
Yes	280(15.7)	<0.001	Prefer not to say	10(17.5)	0.02
Profession			Employment Status		
Non-healthcare	196(19.9)	<0.001	Yes	405(18.2)	<0.001
Unable to get food or water			Profession		
			Healthcare	102(22.6)	<0.001
Unable to get food or water			**Unable to get food or water**		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Age			Nil		
<30	8(1.3)	0.04			
Marital Status					
Unmarried	12(1.5)	<0.001			
Unable to get regular medical care and prescriptions			**Unable to get regular medical care and prescriptions**		
Variable	**N (%)**	**p value**	**Variable**	**N (%)**	**p value**
Employment Status			Nil		
No	9(3.1)	0.04			

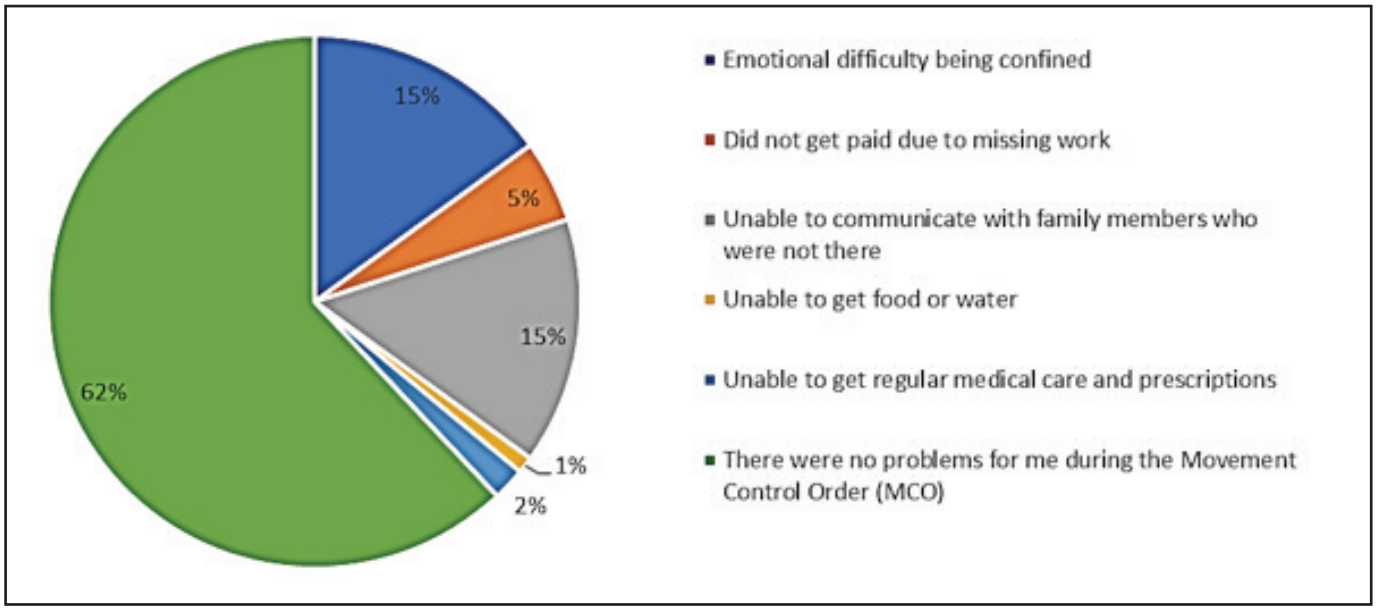

Fig. 1: Percentage of Respondents for "The following was the major problem that I faced during the Movement Control Order (MCO)"

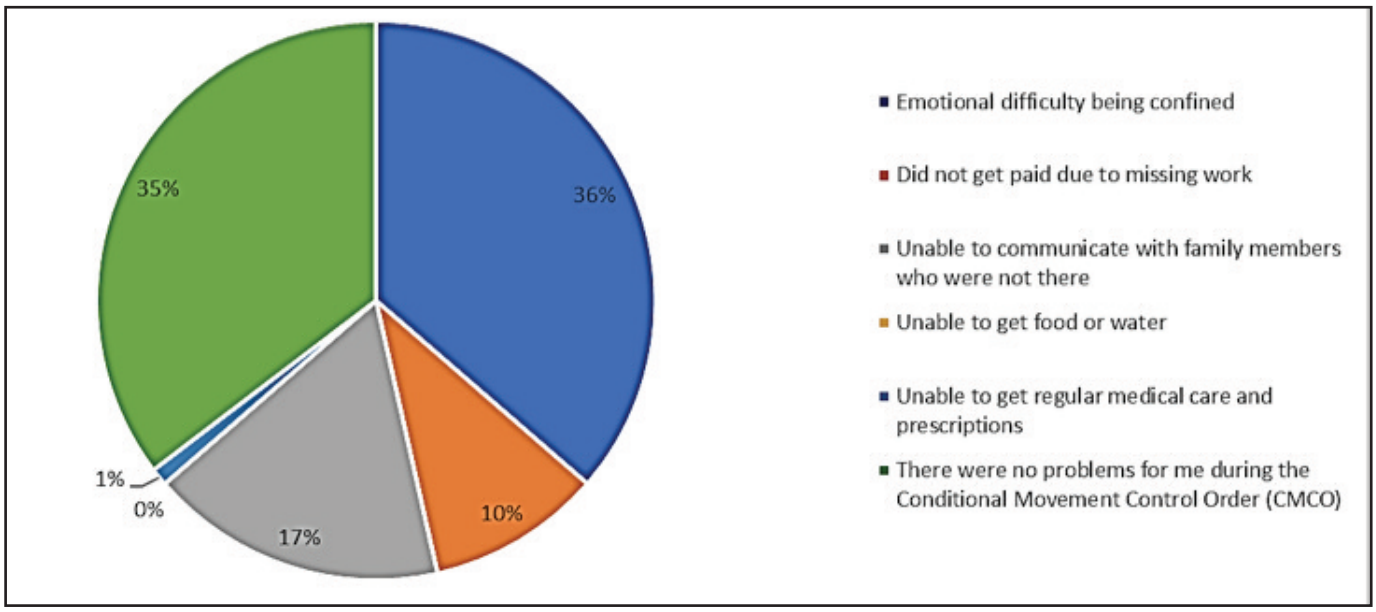

Fig. 2: Percentage of Respondents for "The following was the major problem that I faced during the Conditional Movement Control Order (CMCO)"

facts that these individuals have a more solid support system with their partners. According to Falconier et al.[19], such protective role was more prominent during difficult times, such as financial hardship.

The MCO/CMCO was a major problem for me.

During MCO, participants who were male, unmarried, at primary school, or chose newspaper and TV shows (news, press conference) as their source of information on COVID-19 showed statistically significant agreement with this statement. However, during CMCO, there was an increase in demographic variables groups that found that the movement restriction was a major problem for them: participants who were <30 years old, male, unmarried, at secondary school, unemployed, non-healthcare workers, or chose social media as their source of information on COVID-19. This finding supported duration of quarantine as stressors during quarantine. Studies has revealed that longer durations of quarantine were related with post-traumatic stress symptoms.[10] The longer the lockdown, more group of people were affected. A study done in Malaysia showed that 48% of respondents were experiencing anxiety, 45% of respondents were experiencing depression, and 34% were experiencing stress during this pandemic.[20]

Emotional difficulty being confined.
During MCO, participants who were <30 years old, unmarried, unemployed, or chose newspaper and TV shows (news, press conference) as their source of information on COVID-19 showed statistically significant agreement with this statement. However, during CMCO, only 'unmarried' showed statistical significance. This may be due to the fact that married individuals experienced lower cortisol levels, which suggest lower levels of stress, compared to unmarried and previously married individuals.[18] Participants who were <30 years old had only shown significance during MCO, which may be due to the fact that young people are able to adapt to new environment faster than the older adult.[21] Financial aid given by the government, during MCO, seems to have helped the unemployed.

Did not get paid due to missing work.
Only participants who were male showed statistical significance in this stressor (finance) during both MCO and CMCO. As known, male represented 60.8% of the Malaysian labour as reported in year 2019.[22-23] However due to MCO and CMCO, unemployment was on the rise.[24] Job loss was one of the main factor contributing to 266 reported cases of suicides, where 78% involved were men, during the MCO and CMCO.[25] This could justify that male felt that this was a major problem during both MCO and CMCO.

Unable to communicate with family members who were not there.
It was shocking to know that many respondents agreed to this statement, because, at present, one can communicate with family members and friends who are living abroad and faraway easily with the advancement of information and communication technologies (ICT) especially the Internet. The respondents who agreed to this statement may be referring 'communicate' as 'face-to-face interaction'. In-person contact is still considered the main means of communication with core members.[26] The participants who were employed showed statistical significance during both MCO and CMCO periods. Due to urbanisation, a lot of Malaysian youths migrated from rural to urban areas for more opportunities, higher pay, and better education.[23, 27] However, due to the trend for Malaysians to retire in rural areas, most elderlies in Malaysia reside in rural area.[28] That is why *'balik kampung'* or returning home is a big part of the Malaysian culture. *Balik kampung* is a concept where Malaysian of all ethnic backgrounds embrace returning to natal homes as a social choice during festive seasons.[29] Although currently we are able to communicate with people across the world via technology, the ICT infrastructure facilities, usage, and education in the rural areas are falling behind compared to the urban areas.[27] In addition, past studies have suggested that providing social (emotional/informational) and physical (affection) support is vital to reduce the feeling of loneliness and depression in the Malaysia elderlies.[30-31] With the enforcement of movement restriction, interstate travels were not allowed, thus contributing to the agreement to this statement. Another factor that could support this is the family members who were separated due to working abroad, specifically Singapore. Before the pandemic, more than 300,000 Malaysians, majority of it are Malaysians who work in Singapore, travel via the Johor-Singapore Causeway daily. However due to the border closures by both authorities to curb the spread of the virus, numerous families were separated, and livelihoods lost.[32] This contributes to the loss of 'face-to-face interaction' among family members.

Unable to get food or water and Unable to get regular medical care or prescription.
For these two statements, there were no same groups that had a statistically significance in both the MCO and CMCO period. During the MCO, respondents who were <30 years old and unmarried showed statistical significance in 'unable to get food or water', while the unemployed respondents showed statistical significance in 'unable to get regular medical care and prescriptions. However, eventually, more information regarding the SOPs were shared and regulations were relaxed. This had allowed easy access to these necessities of the people by CMCO.

LIMITATIONS

Although the present study provided a better understanding of the problems faced by Malaysian social media users during the MCO and CMCO period, it has some limitations. Due to the movement restrictions, only participants with Internet access were recruited, and this may limit the findings to those with a higher socioeconomic status and might not be able to reflect the problems faced by the general population. Additionally, this questionnaire was conducted in English; therefore, it limits to Malaysians who could read and understand English. Thus, this study is not an experimental design, the findings are correlative, and we cannot conclude any causal relationship. However, these limitations do not invalidate the seriousness of these findings.

CONCLUSIONS

This study contributes to a better understanding of the problems faced by the Malaysian social media users during these lockdown periods. These findings highlight the need to focus on better policies for the groups (male, unmarried, young, employed) if lockdowns are to be considered in the future.

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Cross-sectional survey on primary care medical doctors' practices on oral health care in pregnancy and its association with knowledge and attitude

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ABSTRACT

Introduction: Oral health care is an important indicator of the overall wellbeing of pregnant women. Optimizing the utilisation of dental care during pregnancy goes a long way in ensuring an improved and optimal pregnancy outcome.

Objective: This study aimed to assess the practices of primary care doctors on oral health care in pregnancy and its association with the level of knowledge and attitude.

Materials and Methods: This cross-sectional study was conducted among primary care doctors in nine public health clinics in Petaling District. A self-administered questionnaire consisting of socio-demographic characteristics, knowledge, attitude, and practices related to oral health care in pregnancy was used.

Results: A total of 138 primary care doctors participated in this study with a response rate of 98.0%. Most primary care doctors frequently advised patients not to delay dental visits until after pregnancy (84.8%), advised patients to see dentists (69.7%), and referred patients to dentists during pregnancy (63.6%). However, only 18.9% perform assessments routinely to detect oral health issues. The median (IQR) score for knowledge was 17(4) (range score: 0–23) and attitude was 23(3) (range score: 6–30). Knowledge median score (p:0.026) and practices of referring patients to dentists (p:0.017) were significantly associated. There was a positive correlation between overall practices of primary care doctors and their age, years of experience, and knowledge.

Conclusion: Most primary care doctors frequently advise and refer pregnant patients to see dentist. Primary care doctors with higher knowledge score, who were older and had more experience, had better overall practices on oral health care in pregnancy.

KEYWORDS:
Oral health, practices, pregnancy, primary care doctor

INTRODUCTION

Oral health plays an essential role in our overall wellbeing. It is estimated that oral diseases affect more than 3.58 billion people worldwide with dental caries being the most prevalent.[1] In Malaysia, based on National Oral Health Survey 2010, the prevalence of dental caries among adults is 89.5% and up to 94% for periodontal disease.[2] Currently, studies on oral health care among pregnant women in Malaysia are still limited.

Oral care is an important but often neglected component during routine pregnancy care. Gingivitis, a precursor to periodontitis, is the most commonly reported oral problem during pregnancy, with a prevalence of 60–75%.[3] During pregnancy, women experience several physiological changes that can adversely affect their oral health. The acidic environment of oral cavity, hyperemesis gravidarum, fluctuations in oestrogen and progesterone level with changes in oral flora, and an increase of sugary diet can lead to poor oral health.[3]

Multiple studies have been conducted on the association of maternal periodontitis with neonatal outcomes. These studies have found a positive association between periodontal disease and poor pregnancy outcomes, such as preterm birth, low birth weight ,and preeclampsia.[4-6] Studies have also shown that mothers with untreated dental caries and severe tooth loss during pregnancy were more likely to produce children who were more prone to dental caries.[7] Besides, periodontal infection is also found to be an additional risk factor for systemic disorders, such as cardiovascular disease, diabetes, and even pulmonary disease.[8]

Despite the potential impact of poor maternal oral health care on both maternal and foetus health and wellbeing, studies of various populations have shown low utilisation of oral health care services among pregnant women.[9-11] In Malaysia, all mothers attending the Maternal and Child Health clinics for antenatal check-ups should be referred to the dental clinic for oral health examination and education as part of a government-driven oral health care program.[12] The report by Ministry of Health Malaysia indicated that the percentage of antenatal mothers who sought dental care in the year 2017 was at only 43%. Despite improvements in dental coverage over the years, the utilisation of dental care among pregnant women remains low especially in the federal territory of Kuala Lumpur (15.3%) and Selangor (17.6%).[12]

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A recent study done by Jamani et al.[11] reported poor knowledge on oral health among pregnant mothers, leading to poor attitude towards dental health during the pregnancy period. Many were unaware that dental caries and gum bleeding could lead to foetal mortality if left untreated. Although most health care providers agreed that maternal oral health care is important,[13] referral practices of doctors were poor.[14-16] Tan et al.[17] reported that oral health care utilisation in Malaysia remains low (13.2%), despite increasing health awareness campaigns. Many perceived that oral health care should only be sought if there are oral health care problems, which are mostly denied. Among health care practitioners, the barriers that impeded referral practices were the lack of knowledge on the safety of dental treatment, insufficient training on oral health, being unaware of the need to refer, and time constraints.[13,18,19]

A study done in India to assess the knowledge, attitude, and practices of primary health providers found that majority agreed that responsibility of preventing oral disease should be incorporated as part of the primary care health system.[20] Primary health care providers, being the first line of pregnancy care support for both urban and rural communities, are in a good position to educate patients on the importance of oral health during pregnancy. They could also increase the chances of dental care utilisation by referring these pregnant women for dental check-ups as part of the pregnancy care. Hence, it is important for primary care doctors to be well equipped with the proper practices and knowledge regarding oral health during pregnancy.

Most existing studies involved patients, hospital-based health care providers, and nurses.[11,17,21,22] To date, many are not aware that oral health care practices are provided by the primary care doctors to pregnant women in Malaysia. Thus, this study aims to bridge the gap and provide insight by exploring the practices of primary care doctors on oral health care during pregnancy and its association with their level of knowledge, attitude, and their socio-demographic characteristics.

Study Design

This cross-sectional study was conducted from October 2019 until December 2019 in nine government health clinics in Petaling District. This district was selected due to its lowest utilisation of dental care among pregnant women in Selangor (JKNS 2019). This study involved medical officers from Klinik Kesihatan (KK) Seri Kembangan, KK Taman Medan, KK Puchong (Batu 14 & 13), KK Kota Damansara, KK Paya Jaras, KK Shah Alam (Seksyen 7 &19), and KK Kelana Jaya. The list of medical officers was obtained from Jabatan Kesihatan Negeri Selangor (JKNS). Based on the data from JKNS, there were 223 medical officers working in the nine government health clinics in Petaling District. Using simple proportion formula for finite population, sample size was calculated based on a prior study that indicated 81% of favourable level of practices,20 95% confidence interval, 5% absolute precision, and 20% non-response rate. Hence, the computed sample size was 140.

The medical officers who fulfilled the eligibility criteria were selected based on simple random sampling using a computer-generated randomiser application (random.org). The inclusion criteria for this study were medical officers who had worked at Maternal & Child Health (MCH) clinics for at least 3 months. Medical officers who were absent during data collection period were excluded from the study.

The questionnaires were handed over to the medical officer in-charge of each clinic by the investigator after a study briefing. The questionnaires were later distributed by the medical officer in-charge to all the selected participants in their respective clinics. A cover letter that explained the study as well as a consent form were attached to each questionnaire. Participants who agreed were asked to sign the informed consent before completing the questionnaire. The questionnaires were collected after one week by the investigator. For those who did not return the form or had incomplete submissions, two follow-ups (face-to-face) were done with one-week interval to collect the remaining questionnaires. All steps and measures conducted in this study followed the values from Helsinki Declaration of conduct of clinical trial.[21]

Study Instrument

This study used a set of self-administered questionnaire comprising two parts. The first part was on the demographic characteristics of the respondents, and the second part covered knowledge, attitude, and practices related to oral health in pregnancy. Questions on socio-demography sought information on respondent's age, gender, average years of experience, acknowledgement of formal oral health training, and information on oral health availability in current practice. The second part of the questionnaires was used in studies conducted by Sharif et al.,[22,23] and permission to use the questionnaires was obtained from the original author. The questionnaire was developed in Bahasa Malaysia and had undergone content validity and reliability testing with the Cronbach alpha value of 0.61–0.76 for knowledge, attitude, and practice domains.[22,23] As the original questionnaire was designed for medical nurses, the set of questionnaires was pre-tested on 30 medical officers from health clinics outside Petaling District. There was no major issue for the doctors to respond to the questions, and the Cronbach alpha for knowledge, attitude, and practice was 0.72, 0.71, and 0.76, respectively, which proved to be equivalent to the original version.

There were 23 items to assess the medical officers' knowledge on oral health care during pregnancy. The answers in the questionnaire consisted of 'Yes' 'No', and 'Do not know' answers in which 1 point was given for the correct answers and 0 point for 'Do not know' or incorrect answers. The total score was the summation of all items that ranged from 0 to 23; the higher the score, the better the knowledge on oral health in pregnancy.

There were six items to assess the medical officers' attitude on the importance of oral health examination and education on antenatal oral health care. These items used five-point Likert scale of responses, ranging from 'strongly disagree' (score 1) to 'strongly agree' (score 5). The negatively worded items were reversely scored, and the total score was the summation of the six items. The total score for attitude ranged from 6 to 30;

Table I: Practices related to oral health (n= 138)

VARIABLES	Very frequent	Frequent	Infrequent	Very infrequent	Never
I advise patients to see a dentist during pregnancy	46 (33.4)	50 (36.2)	30 (21.7)	3 (2.2)	9 (6.5)
I refer patients to dentists for dental check-ups	38 (27.6)	51 (37.0)	26 (18.8)	10 (7.2)	13 (9.4)
I advise patients to delay dental visits until after the pregnancy	3 (2.2)	7 (5.1)	10 (7.2)	5 (3.6)	113 (81.9)
I refer patients to dentists for oral health talks	30 (21.7)	35 (25.4)	32 (23.2)	15 (10.9)	26 (18.8)
I inform patients on the importance of oral health	10 (7.2)	27 (19.6)	36 (26.1)	40 (29.0)	25 (18.1)
I ask patients if they have oral health issues	12 (8.7)	21 (15.2)	49 (35.5)	33 (23.9)	23 (16.7)
I perform assessments to detect oral health issues	11 (8.0)	15 (10.9)	36 (26.1)	37 (26.8)	39 (28.2)

Table II: Knowledge about oral health in pregnancy (n=138)

KNOWLEDGE (CORRECT ANSWER)	CORRECT NO	(%)
Symptoms of gum disease includes :		
• Swollen gums (True)	137	99.3
• Pain from the gums (True)	137	99.3
• Bleeding gums (True)	136	98.6
• Gum abcess (True)	136	98.6
• Bad breath (True)	130	94.2
• Loose tooth (True)	122	88.4
• Changes in gum colour (True)	122	88.4
Gum disease is caused by /associated with		
• Smoking (True)	136	98.6
• Dental plaque (True)	135	97.8
• Pregnancy (True)	112	81.2
• Genetics (True)	61	44.2
• Excessive sugar consumption (False)	6	4.3
• Tooth decay (False)	4	2.9
Acid that cause tooth decay is produced when bacteria react with sugars in carbohydrate (True)	135	97.8
Brushing teeth with fluoridated toothpaste can help prevent tooth decay (True)	127	92.0
Hormonal changes in pregnancy increases the risk for gum disease (True)	121	87.7
Dental treatments during pregnancy may negatively affect the foetus (False)	109	79.0
Stomach acids released during vomiting may erode the surfaces of the teeth (True)	108	78.3
Pregnant mothers should be advised to stop brushing their teeth if the gums bleed (False)	107	77.5
Gum problems in pregnant mothers may result in adverse outcomes such as		
• Low birth weight babies (True)	67	48.6
• Preterm birth (True)	72	52.2
• Cleft lip and palate (False)	53	38.4
Calcium will be drawn out of mothers' teeth by the foetus (False)	40	29.0

Table IIIa: Correlation between overall practices among primary care doctors on oral health care in pregnancy, and their socio-demographic (age and years of experience), knowledge and attitude. (n=138)

Variable	Median (IQR)	r	*p*-value[a]
Socio-demographic			
• Age (years)	34 (4)	0.190	0.026
• Years of experience in primary care	4 (4)	0.216	0.011
Knowledge	17 (4)	0.200	0.020
Attitude	23.0 (3)	0.149	0.082

Spearman correlation test IQR: Interquartile range

Table IIIb: Association between overall practices among primary care doctors on oral health care in pregnancy and their socio-demographic (Gender, Formal education/ training in oral healthcare and having information/brochure on oral healthcare) (n=138)

Variable	Median (IQR)	p value
Socio-demographic		
• Gender		
• Female (n=120)	21 (10)	23 (9)
• Male (n=18)	24 (8)	
Formal education/training on oral health care during pregnancy		
• Yes (n=6)	24.5 (7)	0.544[b]
• No (n=132)	24 (8)	
Information/brochures on oral health during pregnancy' in your practice		
• Yes (n=34)	25 (4)	0.403[b]
• No (n=104)	23 (9)	

b: Mann- Whitney test

Table IV: Practices of advising and referring to dentist for dental check-up during pregnancy and its association with socio-demographic, knowledge and attitude. (n=138)

Variable	Practices of advising patients to see dentist during pregnancy		*p*-value	Practices of referring patients to dentists for dental check-ups		*p*-value
	Frequent (n=96)	Infrequent (n=42)		Frequent (n=89)	Infrequent (n=49)	
Age	34 (4)	33 (4)	0.370[b]	34 (4)	33 (5)	0.125[b]
Gender						
• Female (n=120)	86 (71.7)	34 (28.3)	0.166[c]	81 (67.5)	39 (32.5)	0.060[c]
• Male (n=18)	10 (55.6)	8 (44.4)		8 (44.4)	10 (55.6)	
Years of experience in primary care	5 (4)	3 (4)	0.112[b]	5 (5)	3 (4)	0.051[b]
Formal education/training on oral health care during pregnancy						
• Yes (n=6)	6 (100)	0 (0.0)	0.229[c]	6 (100.0)	0 (0.0)	0.155[c]
• No (n=132)	90 (68.2)	42 (31.8)		83 (62.9)	49 (37.1)	
Information/brochures on oral health during pregnancy' in your practice						
• Yes (n=34)	27 (79.4)	7 (20.6)	0.151[c]	25 (73.5)	9 (26.5)	0.205[c]
• No (n=104)	69 (66.3)	35 (33.7)		64 (61.5)	40 (38.5)	
Knowledge median (IQR)	18 (3)	17 (4)	0.026[b]	18 (3)	17 (4)	0.017[b]
Attitude median (IQR)	24 (4)	23 (3)	0.338[b]	24 (5)	23 (3)	0.438[b]

b: Mann- Whitney test c: chi square

the higher the score, the better the attitude towards providing the oral health care service.

There were seven items to assess the medical officers' practices of advising, referring, and examining pregnant patients with oral health issues. These items used five-point Likert scale of responses, ranging from 'never' (score 1) to 'very frequent' (score 5). The negatively worded items were reversely scored, and the total score was the summation of the seven items. The total score for practice ranged from 7 to 35; the higher the score, the better the practices of providing the oral health care.

Data analysis

Data was input into IBM SPSS version 23. For descriptive statistics, mean (standard deviation) or median (inter quartile range) would be used where appropriate. Categorical variables were described in frequency (n) and percentage (%). Spearmen's correlation and Mann-Whitney test (non-parametric test) were used to determine the associations between the overall practices of providing the oral health care with knowledge, attitude, and socio-demographic characteristics. We also tested the association between the practice of advising to see dentists and referring patients to dentists (categorical) with knowledge, attitude, and socio-demographic characteristics using Chi-square test or Mann-Whitney test. Chi-square test was used for categorical variables, and Mann-Whitney test was used for continuous variables.

The responses for these two items (advising and referring) were re-grouped into two categories, in which 'very frequent' and 'frequent' responses were grouped as 'frequent' and 'infrequent', 'very infrequent', and 'never' were grouped as 'infrequent'. The probability value of less than 0.05 was set as statistically significant.

RESULTS

Characteristics of the Participants

Out of the 140 questionnaires that were distributed, a total of 138 questionnaires were returned, yielding a response rate of 98%. From the 138 questionnaires, there were no missing data The majority of the respondents were females (87%) with mean age of 34 years. Their mean duration of working experience in primary care clinics was 4 years. Only 4.3% reported receiving training on antenatal oral health care, and only 24.6% had brochures on oral health in pregnancy in their clinic settings.

Practices Related to Oral Health in Pregnancy

The median practice score of the respondents was 24.0 (IQR 8) out of a total score of 35. Table I shows the results on practices related to oral health among the medical officers in Petaling District. Of the seven variables, three practices scored the highest, which are the practices of advising patients to see dentists during pregnancy (69.6%), referring patients to dentists for dental check-up (64.6%), and advising patients not to delay dental visits until after pregnancy (85.5%). It was also observed that asking patients if they have oral health issues (23.9%) and performing oral health assessment (18.9%) scored the lowest.

Knowledge on Oral Health in Pregnancy

The median knowledge score was 17 (IQR 4) out of a total score of 23. Table II describes the knowledge of respondents on oral health in pregnancy. Most respondents knew the symptoms of gum disease (range: 88.4–99.3% correct answers) and that gum disease is associated with dental plaque and smoking (97.8–98.6% correct answers). A high percentage of incorrect responses was recorded on the question that tests their knowledge about calcium being drawn out of the mothers' teeth by the foetus (29.0% correct answers) and on the adverse effects of maternal gum disease on infants (range: 48.6–52.2% correct answers).

Attitude on Oral Health in Pregnancy
The median attitude score of the respondents was 23.0 (IQR 3) out of a total score of 30. Majority of the doctors (97.8%) agreed that oral health examination is an important element in routine antenatal care and that they should update their knowledge on oral health in pregnancy (89.9%). However, only two-third of the doctors agreed that they should be trained to perform oral health screening (64.5%) and only a small percentage (9.4%) agreed that it is their responsibility to examine a patients' mouth to detect oral health issues.

Association of Practices Related to Oral Health with Socio-Demographic Characteristics, Knowledge, and Attitude
Tables IIIa and IIIb show the association between the practices of providing oral health care in pregnancy with the socio-demographic characteristics, knowledge, and attitude. There is a significant correlation between overall practices and age, years of experience, and level of knowledge on oral health care during pregnancy. The observed correlation coefficient, r, suggests positive and weak correlations.

Participants who are older or with more years of experience or those with higher level of knowledge had better overall practices on oral health care in pregnancy.

Table IV shows the association between the practices of advising and referring pregnant women for dental check-up and socio-demographic characteristics, knowledge, and attitude of the primary care doctors. Results showed statistically significant associations between these practices and their median knowledge score. No associations were seen with other variables.

DISCUSSION

This study assessed the practice of primary care doctors on oral health care in pregnancy. It further explored the association of their practice with their level of knowledge, attitude, and socio demographic characteristics. This study found that 69.6% of the doctors advising antenatal mothers to see dentists and 64.5% of them referring them. There was a positive correlation between overall practices of primary care doctors and their age, years of experience, and knowledge.

Oral health care practices by the primary care doctors
The findings on practices of medical officers in this study showed distinct patterns on advising and referring patients for further dental care. Two-third of doctors advised patients to see dentist during pregnancy (69.6%), while only a small percentage advised pregnant patients to delay dental visit until delivery (14.5%). This study showed a better practice compared to a study done among physicians in Jordan where only 49% advised their patients to visit dentist and a majority of them (88%) advised their patients to delay dental treatment until delivery.[14] This is probably due to the fact that up to 68% of the physicians in the study were doubtful about the safety of dental treatment during pregnancy[14] in contrast to our study where only 22% believed that dental treatments during pregnancy may affect the foetus.

On the practice of referring patients, 64.6% of the primary care doctors referred patients to dentists for dental check-up. These findings are higher than a previous study conducted in Gujarat, India, which found that only 47.7% of the doctors referred their antenatal patients to the dentists.[16] This is perhaps since dental care services are only available in few states in India at the primary health care level. In addition to this, patients must fund their own dental treatment regardless of public or private practices.[24] This contrasts with our study setting where the majority of the health clinics had on-site dental facilities.

Additionally, in Malaysia, efforts have been made to ensure all pregnant patient attending maternal and child health clinics to be referred to a dentist during their pregnancy as part of routine antenatal check-up.[25] That being said, even though all pregnant women are required to be referred for dental care, there is currently no standard referral procedure in place. This results in non-standardised practices in terms of determining how the referral needs to be made as demonstrated by this study. This situation would benefit with a standardised practice for primary health care providers to refer patient for oral health assessment.

Factors associated with the provision of oral health care
This study found that there is a positive correlation between the respondent's age, working experience, and knowledge with their overall practices on oral health care during pregnancy. The correlation between practices and age and working experience indicates that older primary care doctors with longer working experiences have higher practice scores. One likely explanation for this may be that doctors with more working experience have had better exposure and would have built up a good interdisciplinary relationship over time.[26] However, in terms of the practice of advising and referring pregnant patients for dental care, no association was found between practices and age or working experience. This contrasts with a study done in Brazil,[27] which found the length of working experience is correlated with their referral practices for dental examinations. This difference could be due to the fact that majority of doctors from the mentioned study had more than 15 years of experience compared to our study where majority of them had less than 5 years of working experience.

Most of the primary care doctors showed a good level of knowledge on oral health in pregnancy; however, certain aspects, such as calcium being drawn out from the mother`s teeth and the impact of gum disease on the foetus, need to be revisited. The knowledge on calcium and its metabolism during pregnancy was poorer compared to other studies.[18,14] This was probably due to the existing misconception that calcium will be drawn out of mother's teeth for the development of foetus.[13] Almost half of the doctors scored poorly to the question regarding gum disease and its adverse outcome to the foetus. This is in line with other studies conducted among health care providers where only 44.5–60.9% were able to identify periodontal disease as one of the risk factors for low birth weight and preterm birth.[26,27,17] This shows that despite extensive studies, the awareness levels of doctors are still poor in this aspect. The primary care doctors may benefit from continuous medical education by focusing on gum disease and its adverse outcomes during pregnancy. Primary care doctors who attended educational seminars on oral health care showed much improvement on

their knowledge.[28] It is hopeful that these learnings from continuous medical education will be passed on to pregnant patients as one of the efforts to improve dental care utilisation. With regard to the correlation between knowledge and practices, primary care doctors with higher knowledge had a better overall practice on oral health care in pregnancy. The positive association was also applied to the practice of advising and referring pregnant patients for dental care with the level of knowledge.

In terms of attitude, majority of the doctors agreed that oral health examination is an important element in routine antenatal care and that they should update their knowledge on oral health care. Despite that, a high percentage of the primary care doctors (81%) believe that it is not their responsibility to detect oral health problems. This is in line with their practice where only one-fifth of primary care doctors frequently performed assessment to detect oral health issues, ask patients regarding oral health issues, and inform pregnant women on the importance of oral health care. This finding is similar to another study,[13] which agreed that oral assessments during antenatal visits is important, although conducting oral examination during pregnancy is outside their routine practice. Insufficient training on providing basic oral examination, lack of knowledge and skills to educate patients, and lack of time were some of the barriers identified.[18,13]

One of the limitations of this study is that this study only focused on doctors serving the government health care clinics and not involving private clinics doctors. The demographic characteristics of the respondents in this study are fairly comparable to the National Health Care Statistic of primary care doctors in Malaysia as of year 2014 whereby a majority of the respondents were female, between the ages of 28 and 34 years with less than 5 years of working experience in a public primary care setting.[29] However, as this study was conducted in a particular geographic region, generalizing the results as a representation of a larger population needs to be judicious. The study instrument was a self-administered questionnaire, and participants were given a period of 1–2 weeks to answer the questionnaire; hence, there were no direct observation done, thus reliant on the respondents' reliability in recalling as well as their honesty. Besides, as this study did not include the barriers faced by the primary care doctors in their practices on oral health care in pregnancy, little is known on the limitation faced from the perspective of the primary care doctors.

CONCLUSION

This study shows that the overall practices among primary care doctors were encouraging with 'the practice of advising and referring pregnant women for dental care' scoring the highest in comparison to other practices that were measured. There was also an association between overall practices and age, years of experience, and knowledge. Continuous medical education plays a vital role as the catalyst in improving and enforcing the knowledge among primary care doctors as part of the effort in strengthening their practices. Therefore, it is recommended to increase the knowledge and awareness of oral health care among primary care doctors by continuously educating through collaboration with dental professionals as part of antenatal care.

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ETHICAL CONSIDERATION

Approval to conduct the study (without funding) was obtained from the Medical Research and Ethic Committee (MREC) of the Ministry of Health Malaysia (NMRR-18-3900-44889) and the Research Ethic Committee of Universiti Kebangsaan Malaysia (PPUKM FF-2019-148). Permission was then obtained from the Selangor State Health Department, Petaling District Health Office, and Family medicine specialist from the respective health clinics, Participants (medical professionals) were explained regarding the nature of the study, and written consent was obtained before answering the questionnaire.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Foot care knowledge and self-care practices among diabetic patients in Penang: A primary care study

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ABSTRACT

Introduction: In Malaysia, the prevalence of diabetes mellitus has been increasing annually, currently affecting 18.3% of the population. Diabetic foot ulcer, a common complication of diabetes, is associated with high morbidity and mortality, consequently increasing health care expenditure. A previous study showed that foot care knowledge and foot self-care practices help to reduce the development of ulcers.1,2 This study aims to identify the level of foot care knowledge and self-care practices among diabetic patients in the primary care setting. Objective: This study was to determine the level of foot care knowledge and foot self-care practices among diabetic patients in the primary care setting in Penang Island and its determinants and the correlation between level of foot care knowledge and self-care practices among diabetic patients.

Material and Methods: A cross sectional study was performed on 311 diabetic patients who were registered to two government health clinics in Penang. Information regarding respondents' demographic status, foot care knowledge, and foot self-care practices were gathered using a self-administered questionnaire. Data were analysed using the Statistical Package for the Social Sciences (SPSS) 22. The Mann–Whitney U test and Kruskal–Wallis test were applied to the analysis. Multiple linear regression was performed to identify the determinants. Correlation between knowledge and self-care practice was determined using the linear regression model.

Results: One hundred and sixty-five (53.1%) respondents achieved good knowledge scores and 196 respondents (63%) achieved good self-care practice scores. The median age of respondents was 61 years, who were mostly females (56.6%), Malays (41.2%), and unemployed (48.6%). Median HbA1c level was 7.5%, and 42.8% of respondents had diabetes for 5 to 10 years. Lowest scores for knowledge and self-care practices were observed in foot skin care questions. Formal foot care education was found to be a significant predictor of foot care knowledge ($p<0.05$, 95% CI −1.102, −0.098). Foot care knowledge was significantly and positively correlated with foot self-care practices ($p<0.001$, 95% CI 0.548, 0.727).

Conclusion: Foot care knowledge has significant positive correlation with foot self-care practices. Empowering diabetic patients with foot care knowledge may lead to significantly better foot self-care practices.

KEYWORDS:
Diabetic foot, self-care, primary health care, foot care knowledge

INTRODUCTION

According to the National Health Mortality and Morbidity Survey 2019 report, the prevalence of diabetes mellitus among Malaysians has increased from 13.4% in 2015 to 18.3% in 2019.[3] In Penang, the figures are similarly worrying with 18.1% in 2015 and 18.3% in 2019.[3] Diabetic foot ulcer, a common complication of diabetes, is associated with high morbidity and mortality, consequently increasing health care expenditure. Diabetic foot ulcer causes more than 80% of non-traumatic limb amputations and has a 50% mortality rate within 5 years of onset.[4] Overall financial cost of type 2 diabetes mellitus management was recorded to reach RM 1.4 billion in 2011, which corresponded to 9.21% of the Malaysian Ministry of Health's budget.[5] Treatment of an acute diabetic foot infection in a single hospital admission is approximately RM 190 per patient per year.[6]

Studies have shown that diabetic foot care knowledge and foot self-care practices are able to reduce the incidence of diabetic foot ulcers.[1,2] Therefore, foot self-care practices are greatly encouraged to prevent and delay potential complications such as limb amputations.[7,8] Goweda et al. reported that foot self-care practice also reduces common foot problems such as corns and callosities and facilitates the healing of foot ulcers.[7] Despite having profound effects on preventing foot complications, foot care knowledge and foot self-care practices are still inadequate among diabetic patients worldwide.[9,10] A local study in a tertiary centre in Terengganu had reported that patients had substantially poor foot care knowledge and self-care practices.[11] However, no studies had looked into the primary health care centres where majority of the diabetic patients come for their follow-up.

In view of minimal data from primary care facilities, this study aims to determine the level of foot care knowledge and

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foot self-care practices among diabetic patients in primary care, Penang. This study also establishes the factors associated with level of foot care knowledge and foot self-care practices and the correlation between the two.

MATERIALS AND METHODS

Study site

Two health clinics in Penang were selected for the study. Both represent the urban population of Penang Island and the largest clinic in each district.

Subjects and data collection

A cross-sectional study was conducted between August 2019 and February 2020 among diabetic patients attending a public health clinic located in the North-East District and another public health clinic located in the South-West District of Penang Island. Diabetic patients who were 18 years and above, registered with the National Diabetes Registry, and able to understand either English or Malay language were enrolled into the study. Those who were blind, illiterate, pregnant, cognitively impaired, and having debilitating mental illness were excluded from the study.

A validated questionnaire in English developed by Hasnain et al.[12] was adopted to assess the level of foot care knowledge and self-care practices among the respondents. This questionnaire was pre-tested in the study, with further validation done by Almuhanadi et al.[13] and Magbanua et al.[14] via content and face validation. In the local setting, the questionnaire by Hasnain et al.[12] was adopted and validated by Lutfi et al.[11] in Terengganu and Kamaru et al.[15] from UKM Medical centre. The questionnaire was translated from English to Malay language by two independent individuals and back translated to English by a different pair of independent individuals. All were well versed in both languages. Discrepancies in the translation were then discussed to achieve the most suitable and comprehensive Malay language version.

The questionnaire comprises two sections. The first section collected socio-demographic and clinical information of each respondent. These included age, gender, race, occupation, education level, household income, and marital status, whereas the clinical profiles obtained data regarding concomitant medical problems, duration of diabetes, types of medication, glycaemic control, past and current foot abnormalities or complications, and prior exposure to diabetic foot care education. The second section consisted of 15 'yes' or 'no' questions regarding foot care knowledge and foot self-care practices. Each correct answer was given one mark. The points were then added up for each of the foot care knowledge and foot self-care practices categories. Higher scores signified better foot care knowledge and foot self-care practices. The level of good knowledge and good practice was determined based on the median score of each category. Scores greater than the median were considered as good, and scores lower than the median were considered as poor.

A pilot study was conducted on 75 respondents. Reliability analysis showed Cronbach's Alpha value of 0.732 for knowledge score. However, for practice score, the Cronbach's Alpha value was 0.585. After omitting Item 9 in the practice score questions, Cronbach's Alpha value improved to 0.689. Hence, Item 9 in foot self-care practice was not included in the subsequent analysis. Item 9 in the foot self-care practice questionnaire examines the respondents' habit to change their socks every day. This question might not be relevant in our local context as our community probably does not have the habit of wearing socks due to our tropical climate.

The sample size was determined by assuming that the prevalence of foot care knowledge is 29.3% and prevalence of good diabetic foot practice is 14%, as noted in the reference article by Hasnain et al.12 Sample size was calculated using G*Power online application version 3.1.9.2 and a minimum of 310 subjects was required for this study based on 5% significance level and a power of 80% with a 95% confidence interval.

The sample units were recruited using systematic random sampling. A sample interval of 1:10 was derived by dividing the estimated study population with the estimated sample size (3968/372). Diabetic patients who came for follow-up appointments were listed daily to aid in recruitment. The first sample was selected by using a computer-generated random number. Subsequently, every 10th name from the list was approached to be recruited as samples. This went on until the sample size was met.

The researcher approached the selected patients individually and screened them for eligibility. Those who did not fulfil the inclusion criteria or refused to participate were replaced by the following 10th name on the list. Eligible respondents were given verbal and written information regarding the study. After obtaining consent, respondents were required to fill in the questionnaire. Clarification on questions was done only when confusion arose. Respondents' clinical profiles were collected from their medical records. After completing the questionnaire, the respondents underwent a foot examination to identify the presence of diabetic peripheral neuropathy, peripheral arterial disease, diabetic foot ulcers, and other abnormalities. Examination includes inspection for the presence of foot ulcers or deformity, palpation for temperature and pulses, and sensory testing with monofilament and tuning fork.

Ethical approval

Ethical clearance was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. This study was also registered under the National Medical Research Register (NMRR ID: NMRR-18-3914-44917).

Statistical analysis

Statistical Package for Social Sciences (SPSS) software version 22.0 was used for analysis. Normality testing was performed for all continuous data before proceeding to descriptive analysis. The results were reported as median and interquartile range (IQR) as the data were not normally distributed. The Mann–Whitney U test and Kruskal–Wallis test were conducted on categorical variables to ascertain their association with the knowledge and practice scores. The associations between age, duration of diabetes, and HbA1c values with knowledge and practice scores were analysed

Table I: Socio-demographic and clinical background data of respondents

Variable	N (%)	Median (IQR)
Age (in years)		61.0 (14.0)
21–40	23 (7.4)	
41–60	131 (42.1)	
61–80	153 (49.2)	
81–100	4 (1.3)	
Gender		
Male	135 (43.4)	
Female	176 (56.6)	
Race		
Malay	128 (41.2)	
Chinese	117 (37.6)	
Indian	63 (20.3)	
Others	3 (1.0)	
Level of education		
Not schooling	14 (4.5)	
Primary school	72 (23.2)	
Secondary school	179 (57.6)	
College/University	46 (14.8)	
Employment		
Employed	113 (36.3)	
Unemployed	151 (48.6)	
Retired	47 (15.1)	
Hba1c (%)		7.5 (2.4)
<7.0	104 (33.4)	
7.0–8.5	101 (32.5)	
>8.6	97 (31.2)	
Diabetic treatment		
OHA only	223 (71.7)	
OHA and insulin	72 (23.2)	
Insulin only	10 (3.2)	
Diet control	6 (1.9)	
Current foot ulcer		
Yes	9 (2.9)	
No	302 (97.1)	
History of foot ulcer		
Yes	24 (7.7)	
No	287 (92.3)	
Foot deformity		
Yes	10 (3.2)	
No	301 (96.8)	
Diabetic complications		
Retinopathy	36 (11.6)	
Neuropathy	13 (4.2)	
Vasculopathy	38 (12.2)	
None	205 (65.9)	
Others	19 (6.1)	
Formal foot care education		
Yes	170 (54.7)	
No	141 (45.3)	
Duration of diabetes (in years)		8.0 (8.0)
<5	90 (28.9)	
5–10	133 (42.8)	
11–15	47 (15.1)	
>15	41 (13.2)	
Underlying medical problems		
Hypertension	66 (21.2)	
Dyslipidaemia	38 (12.2)	
Hypertension and dyslipidaemia	161 (51.8)	
None	43 (13.8)	
Others	3 (1.0)	

Note. OHA: Oral Hypoglycemic Agent

Table II: Questions determining the foot care knowledge and practice

Foot care measures	Knowledge (N = 311)	Practice (N = 311)
1. Importance of taking anti-diabetic medications to prevent complications	311 (100%)	289 (92.9%)
2. Daily inspection of feet	236 (75.9%)	235 (75.6%)
3. Using warm water for washing/bathing	231 (74.3%)	216 (69.5%)
4. Checking the temperature of the water before using	220 (70.7%)	199 (64.0%)
5. Drying the feet after washing	287 (92.3%)	271 (87.1%)
6. Talcum powder usage for keeping interdigital spaces dry	133 (42.8%)	101 (32.5%)
7. Applying lotion to keep the skin soft to prevent dryness	235 (75.6%)	195 (62.7%)
8. Lotion not to be applied in the interdigital spaces	136 (43.7%)	166 (53.4%)
9. Trimming toenails straight with care	274 (88.1%)	258 (83.0%)
10. Daily washing of feet	304 (97.7%)	298 (95.8%)
11. Wearing comfortable court shoes	276 (88.7%)	297 (95.5%)
12. Checking the inside of the shoes before wearing	283 (91.0%)	277 (89.1%)
13. Not walking barefoot	271 (87.1%)	264 (84.9%)
14. Warning signs for which consultation is required	278 (89.4%)	291 (93.6%)

Table III: Factors associated with levels of diabetic foot care knowledge and foot self-care practice

Item	n	Foot care knowledge score Median (IQR)	p value	Foot care practice score Median (IQR)	p value
Age (in years)[2]			0.485		0.827
21–40	23	10.0 (4.0)		11.0 (3.0)	
41–60	131	12.0 (3.0)		12.0 (3.0)	
61–80	153	12.0 (3.0)		11.0 (3.0)	
81–100	4	12.0 (8.0)		12.0 (6.0)	
Gender[1]			0.490		0.089*
Male	135	12.0 (3.0)		11.0 (3.0)	
Female	176	12.0 (3.0)		12.0 (3.0)	
Race[2]			0.229*		0.021*
Malay	128	12.0 (3.0)		12.0 (3.0)	
Chinese	117	12.0 (4.0)		11.0 (3.0)	
Indian	63	12.0 (3.0)		11.0 (3.0)	
Others	3	13. 13.0 (2.0)		14. 14.0 (.)	
Level of education[2]			0.612		0.314
Not schooling	14	11.5 (6.0)		10.0 (4.0)	
Primary school	72	12.0 (2.0)		12.0 (3.0)	
Secondary school	179	12.0 (3.0)		11.0 (3.0)	
College/University	46	12.0 (3.0)		11.0 (3.0)	
Employment[2]			0.499		0.809
Employed	113	11.0 (3.0)		11.0 (3.0)	
Unemployed	151	12.0 (3.0)		12.0 (3.0)	
Retired	47	12.0 (3.0)		11.0 (3.0)	
Hba1c (%)[2]			0.619		0.336
<7.0	104	12.0 (3.0)		11.0 (3.0)	
7.0–8.5	101	12.0 (3.0)		12.0 (3.0)	
>8.6	97	12.0 (3.0)		11.0 (3.0)	
Diabetic treatment[2]			0.472		0.579
OHA only	223	12.0 (3.0)		11.0 (3.0)	
OHA and insulin	72	11.0 (3.0)		12.0 (3.0)	
Insulin only	10	11.5 (4.0)		11.5 (3.0)	
Diet control	6	12.0 (3.0)		12.0 (2.0)	
Current foot ulcer[1]			0.511		0.897
Yes	9	12.0 (5.0)		10.0 (4.0)	
No	302	12.0 (3.0)		11.0 (3.0)	
History of foot ulcer[1]			0.941		0.226*
Yes	24	11.5 (4.0)		12.0 (3.0)	
No	287	12.0 (3.0)		11.0 (3.0)	
Foot deformity1			0.535		0.562
Yes	10	12.0 (5.0)		11.0 (4.0)	
No	301	12.0 (3.0)		11.0 (3.0)	
Diabetic complications2			0.356		0.103*
Retinopathy	36	12.0 (2.0)		11.0 (3.0)	
Neuropathy	13	11.0 (5.0)		10.0 (4.0)	
Vasculopathy	38	11.0 (4.0)		10.5 (4.0)	
None	205	12.0 (3.0)		11.0 (3.0)	
Others	19	12.0 (3.0)		11.0 (4.0)	

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Table III: Factors associated with levels of diabetic foot care knowledge and foot self-care practice

Item	n	Foot care knowledge score Median (IQR)	p value	Foot care practice score Median (IQR)	p value
Formal foot care education[1]			0.023*		0.004*
Yes	170	12.0 (3.0)		12.0 (3.0)	
No	141	11.0 (2.0)		11.0 (4.0)	
Duration of diabetes (in years)[2]			0.742		0.556
<5	90	11.0 (3.0)		11.0 (3.0)	
5–10	133	12.0 (3.0)		11.0 (3.0)	
11–15	47	12.0 (3.0)		12.0 (3.0)	
>15	41	12.0 (2.0)		12.0 (3.0)	
Underlying medical problems[2]			0.757		0.636
Hypertension	66	12.0 (3.0)		11.0 (3.0)	
Dyslipidaemia	38	11.0 (3.0)		11.0 (4.0)	
Hypertension and dyslipidaemia	161	11.0 (3.0)		12.0 (3.0)	
None	43	11.0 (3.0)		11.0 (4.0)	
Others	3	8. 8.0 (.)		10. 10.0 (.)	

[1]Mann–Whitney test [2]Kruskal–Wallis test

* Variables with p<0.25 were selected for multiple linear regression analysis.

Table IV: Multiple linear regression analysis to determine the predictors of foot care knowledge and self-practice

Variable	Regression coefficient *b* (95% CI)	Standardised regression coefficient *b*	*t*	*p*
Foot care knowledge				
Race	– 0.212 (– 0.530 to 0.106)	– 0.074	– 1.312	0.190
Formal foot care education	-0.600 (– 1.102 to – 0.098)	– 0.133	– 2.351	0.019
Foot care self-practice				
Race	0.217 (– 0.041 to 0.474)	0.074	1.656	0.099
Gender	0.271 (– 0.135 to 0.676)	0.058	1.313	0.190
History of foot ulcer	– 0.367 (– 1.125 to 0.391)	– 0.042	– 0.953	0.341
Diabetic complications	0.121 (– 0.070 to 0.312)	0.056	1.244	0.215
Formal foot care education	– 0.333 (– 0.749 to 0.082)	– 0.072	– 1.580	0.115
Foot care knowledge	0.638 (0.548 to 0.727)	0.621	14.001	0.000

using Spearman's rho. Factors with p<0.25 in bivariate analysis were subsequently analysed with multiple linear regression (MLR). The results of the MLR were presented as coefficient and 95% confidence intervals. Linear regression was performed to determine the correlation between foot care knowledge scores and practice scores. Significant level was set at p<0.05.

RESULTS

We approached 332 eligible diabetic patients, of which a total of 311 patients agreed to participate in this study giving a response rate of 93.7%.

Table I describes the sociodemographic data of this study. The median age (IQR) of our study participants was 61 years (IQR 14). Most of them were females (56.6%), Malays (41.2%), and unemployed (48.6%). Out of 311 patients recruited, 133 (42.8%) had diabetes for 5 to 10 years with the median HbA1c of 7.50% (IQR 2.4).

A large majority of them (71.7%) were using only oral hypoglycaemic drugs, while 26.4% were using insulin either alone or with oral hypoglycaemic drugs. At the time of study, 3.2% of them had foot deformity and 2.9% had ongoing foot ulcer.

In this study, knowledge scores ranged from 3 to 14 with a maximum possible score of 14. The median score was 12.0 (IQR 3), and 165 (53.1%) respondents were categorised as having good knowledge scores. However, for foot self-care practices, the scores ranged from 3 to 14. The median score was 11.0 (IQR 3), with a higher number of respondents (196 respondents, 63%) achieving good practice scores.

Table II shows the responses to questions regarding foot care knowledge and practices. The responses for each foot care measure were generally good with exception for talcum powder usage to keep interdigital spaces dry and avoidance of lotion application in interdigital spaces. The former scored the lowest positive response of 42.8% for knowledge and 32.5% for practice, while the latter scored 43.7% for knowledge and 53.4% for practice. Patients gave a relatively good response to applying lotion to prevent dryness with 75.6% for knowledge, but only 62.7% for practice.

Table III exhibits the median score of both foot care knowledge and foot care practice according to each variable and their strength of association. Race and formal foot care education show p value of less than 0.25 for foot care knowledge score. As for foot care practice score, race, gender, history of foot ulcer, diabetic complications and formal foot care education demonstrate p value of less than 0.25. These variables were further analysed with multiple linear regression analysis.

In this study, there was no multicollinearity between the independent variables in which the tolerance values were more than 0.1 and variance inflation factor (VIF) values were less than 5.

Table IV reports on the predictors for foot care knowledge and self-practice. Formal foot care education was found to be a significant predictor of foot care knowledge ($p<0.05$, 95% CI −1.102, −0.098). Foot care knowledge was seen to be significantly and positively correlated with foot self-care practices ($p<0.001$, 95% CI 0.548, 0.727).

DISCUSSION

More than half of the respondents achieved good knowledge (53.1%) and good practice (63.0%) scores. This is in line with the percentage of formal foot care education received by the study population where more than half of them (54.7%) were found to have received formal advice on foot care practice in the past. Furthermore, all diabetic patients in primary care settings undergo annual foot examination and counselling by diabetic educator. This has also helped in improving patients' awareness of diabetic foot self-care. Conversely, Lutfi et al.[11] found substantially poor foot care knowledge and foot self-care practices among in-patient respondents, which could be attributed to the fact that their study population was based on a tertiary centre where the respondents were admitted for diabetic foot complication. Hence, it explains the lower knowledge and practice scores among the participants. Interestingly, Kamaru et al.[15] demonstrated a high percentage for good knowledge level (90.1%) but poor scores for practice level (6.2%) among a subset group of elderly patients who attended University Kebangsaan Malaysia Medical Centre (UKMMC). The contrast between the studies may be due to varying implementation of diabetic education programmes. UKM being a teaching hospital would have a more comprehensive screening and education programme for their diabetic patients, thus leading to a higher knowledge score. However, the poor practice of diabetic self-care among the elderly needs to be further explored as our study did not demonstrate age as a significant determinant for self-care practice.

Compliance to medications to prevent complications and foot washing ranked the top scores in assessing respondents' knowledge. All agreed that the importance of taking anti-diabetic medications is to prevent complications. A tertiary centre study in Malaysia observed 93.6% correct responses[11] while in Pakistan, Hasnain et al.[12] reported 78% correct responses regarding importance of taking anti-diabetic medications. This may be due to lack of medical knowledge and awareness because 48.7% of respondents in Hasnain et al.'s[12] study were illiterate. For foot washing, 95.8% respondents in this study knew to wash their feet daily and 92.3% were aware to dry their feet after washing. This was also seen by Lutfi et al.[11] and Magbanua et al.[14] who reported a higher percentage of respondents for both knowledge of daily washing of feet and drying of feet after washing. Several studies conducted in Muslim countries, such as Jeddah, Pakistan, and Makkah, also reported high number of respondents for daily washing of feet, and they are related to the act of ablution performed daily by muslims.[7,12,16] In this study, 41.2% of respondents are Muslims, and ablution may have played a role in the high percentage of this practice.

Less than half (42.8%) knew about the use of talcum powder to keep interdigital spaces dry, and only 43.7% knew to avoid applying lotion at interdigital spaces. Many other studies observed similar findings as well.[11,12,14,17] This implies that across the Asian countries, little emphasis is placed upon educating diabetic patients regarding foot skin care. Magbanua et al.[14] commented that people of Philippines mostly wear slippers and so the use of talcum powder to keep interdigital spaces dry seemed unimportant. Compared to Lutfi et al.[11] and Magbanua et al.,[14] our respondents scored better in knowledge of foot washing, in terms of checking water temperature (70.7%) and using warm water for washing or bathing (74.3%). Lutfi et al.[11] and Magbanua et al.[14] observed lower scores for knowledge of using warm water for washing at 47.8% and 31.5%, respectively. Magbanua et al. mentioned that water temperature control is largely unavailable in Philippines, and it is a local norm to use tap water without checking the temperature.[14]

As for the practice of foot care, 97.7% of respondents washed their feet daily and a similar attitude was also reported by previous studies.[8,11,12,14] In this study, drying the feet after washing and taking anti-diabetic medications to prevent complications showed lower practice level compared to knowledge level. This reflects poor compliance among the respondents regardless of having good knowledge of foot care. However, a contrary relationship was seen for the behaviour of seeking doctor's consultation. The knowledge of warning signs to seek doctor's consultation was 89.4%, but its practice was higher at 93.6%. This implies that respondents have safe health seeking behaviour.

A low number of respondents (32.5%) were using talcum powder to keep interdigital spaces dry, and slightly more than half (53.4%) of them avoided applying lotion at interdigital spaces. These two items had the lowest percentage for knowledge and practices. Hasnain et al.[12] and Pourkazemi et al.[17] showed even worse responses with a percentage of less than 5% for the practice of using talcum powder to keep interdigital spaces dry. This could be due to the dry and dusty climate in Pakistan (Hasnain et al.) and Iran (Pourkazemi et al.), which makes applying talcum powder to keep toes dry

seemed unimportant. Across the various studies, knowledge and practice of foot skin care are as poor, which is similarly observed in this study. Hence diabetic foot care education needs to emphasise more on methods to maintain healthy skin. For foot washing, our respondents had relatively low scores as only 64% respondents checked water temperature and 69.5% used the correct water temperature. This finding was much better than what was found on the east side of Malaysia.[11] This could be due to the lack of a water temperature control system in the household.

This study has found no significant association between patient's demographic factors with level of foot care knowledge and practice. This could be attributed to the smaller sample size compared to other larger studies that found that level of education, gender, occupation, and age had significant association with respondent's foot care practices.[16-18] Clinical backgrounds such as duration of diabetes, comorbidities, HbA1c, type of diabetic treatment, previous or current foot ulcers, and diabetic complications also did not portray any significant association with foot care knowledge or practice. However, this study observed positive significant correlation between foot care knowledge and foot care practice ($p<0.001$) as seen by Qadi et al.,[16] Li et al.,[18] and Pourkazemi et al.[17] Furthermore, formal foot care education was also seen as a significant predictor for foot care knowledge ($p<0.05$). Thus, empowering diabetic patients with concise foot care knowledge will improve their foot care practices.

STRENGTHS AND LIMITATIONS

This study was conducted in a primary care setting in Malaysia compared to all previous local studies conducted in a tertiary care setting. It is important to carry out the study in a primary care setting because majority of the community attends primary care clinics for chronic disease follow-up. The sample seen in Lutfi et al.[11] and Kamaru Zaman et al.[15] comprised of inpatients representing diabetics with known complications. This study involved diabetics with and without complications. Hence, this study was able to observe a wider spectrum of diabetic patients. Another advantage was that respondents in this study were randomly selected, which is more representative of the community and eliminates the possibility of bias.

However, few limitations were also observed in this study. Firstly, two demographic factors, income and literacy, were not analysed. Income was enquired in the pilot study but yielded very poor reply from the respondents. Hence, it was omitted during the actual study. Illiteracy was an exclusion criterion, and this was a disadvantage to the study as Hasnain et al.[12] found significant relationship between education level and foot care knowledge, with illiterate respondents exhibiting lowest knowledge scores. Secondly, in the questionnaire, most of the questions were formatted to be marked as correct when replied 'yes' instead of 'no'. Respondents may have realised this and prematurely answered 'yes' for all the questions. Thirdly, the study sample only included urban populations as it was conducted in two primary health care clinics in Penang Island. Semi-urban populations in the mainland of Penang were not included in the study. Therefore, a larger sample inclusive of mainland and island populations would be a better reflection of the Penang community.

RECOMMENDATION

The respondents scarcely use talcum powder and rarely avoid lotion application at interdigital spaces. Their knowledge and practice of foot skin care were quite staggering. The prevailing foot care education lacks foot skin care knowledge; hence, it is recommended that foot care education encompasses methods for sustaining healthy skin of the feet. This study shows that acquiring foot care knowledge significantly improves foot care practices. In view of this notion, further research can be conducted to identify methods of effective foot care education, and audits of current foot care education should be implemented regularly at primary care settings.

CONCLUSION

The level of foot care knowledge and foot self-care practice among diabetic patients in the primary care setting in Penang Island is encouraging. This study portrayed a significant positive correlation between foot care knowledge and foot care practices. This proves that acquiring foot care knowledge motivates better foot care practices. Hence, more efforts need to be done to ensure effective delivery of foot care knowledge to all diabetic patients as it leads to a better foot self-care practice, regardless of their socio-demographic and clinical background.

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POTENTIAL CONFLICTS OF INTEREST

None.

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The effect of health education intervention through mobile phone on hypertension patients : A systematic review

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ABSTRACT

Introduction: Hypertension is a silent killer disease that, if not handled properly, will lead to dangerous complications for the patient. Health education through mobile phones can be an intervention used to improve health services and the management of hypertension in the community. This study aims to synthesise research findings on the effect of mobile phone health education interventions on hypertensive patients.

Materials and Methods: A systematic review. Search strategy was conducted on international journal databases, namely Scopus, PubMed, ProQuest, Web of Science, and Science Direct with the keywords 'health education', 'mobile phone' and 'hypertension'. Inclusion criteria using PICOS, namely Population: hypertensive patients, *Intervention:* health education using a mobile phone, *Comparation:* ordinary health education, *Output:* knowledge, attitudes, behaviour, Study design: trial method. The publication year 2017-2021.

Results: There were 145 articles found in the search. Articles were identified and screened resulting in five complete articles that met the inclusion criteria. The results of this study found that health education interventions via mobile phones could increase patient knowledge about hypertension; improve self-management; monitor blood pressure; increase adherence to pharmacological treatment, a hypertensive diet, i.e.,low salt intake, vegetable and fruit intake, and physical activity; decrease blood pressure; and improve quality of life. Health education via mobile phones can also provide the latest information quickly to patients about controlling hypertension, antihypertensive drugs, and health services that can be utilised.

Conclusion: Health education interventions via mobile phones have a significant positive effect in controlling hypertension in the community, but it is necessary to consider the patient's age, socioeconomic status, literacy conditions, and ability to use mobile phones to receive the health education that will be provided.

KEYWORDS:
Health Education, Mobile Phone, Hypertension

INTRODUCTION

Hypertension is a chronic non-communicable disease that still threatens the health and life of people worldwide. Hypertension is one of the silent killer diseases that, if not handled properly, will lead to various dangerous complications for the sufferer. Hypertension is a major risk factor for stroke and cardiovascular disease in individuals.[1]

Non-compliance with treatment and care programs is a risk factor for hypertensive patients who are prone to complications. This condition can occur because patients do not get adequate information about antihypertensive drugs and cannot read information about treatment programs.[2] The self-efficacy of hypertensive patients is caused by various factors related to the success of controlling hypertension. Health promotion efforts must be developed and modified to overcome this situation.[3]

Hypertensive patients perceive nurses as key players in the management of hypertensive patients.[4] Controlling hypertension in the community is a challenge for nurses and requires an effective strategy to provide optimal service.[5] Health services for hypertensive patients should be focused on disease control and secondary prevention of cardiovascular complications. Low patient motivation in treatment programs requires new ways that nurses can use to educate hypertensive patients in efforts to control disease and prevent cardiovascular complications.[6] Adequate nursing monitoring and care are needed to assess patient adherence to the treatment program in reducing the risk of complications and developing weakness syndrome.[7]

Innovation in health and nursing services for hypertensive patients is currently very much needed along with the times and advances in information communication technology based on the internet and cellular telephones.[8] Health education through mobile phones can be one of the latest interventions in health education to improve service quality and disease management for hypertensive patients in the community. The purpose of this study was to determine the effect of mobile phone health education interventions on hypertensive patients.

MATERIALS AND METHODS

Study design

The design of this study is a systematic review conducted with a synthesis of relevant research articles on the effect of mobile phone health education interventions on hypertensive patients using a systematic review PRISMA. This study did not carry out a meta-analysis test process on quantitative data.

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Search strategy
Search for articles was carried out on five international journal databases, namely Scopus, PubMed, ProQuest, Web of Science, and Science Direct. Article searches were conducted using the keywords 'health education', 'mobile phone', and 'hypertension'.

Eligibility criteria
The inclusion criteria in this study included all articles describing the effect of health education conducted using mobile phones on hypertensive patients. The inclusion criteria using PICOS, namely Population: hypertensive patients, Intervention: health education using a mobile phone, Comparation: ordinary health education, Output: knowledge, attitudes, behaviour, Study Design: trial method. The publication year: 2017-2021. The exclusion criteria for articles in this study: research not related to health education by mobile phone, non-hypertensive patients, non-hypertensive education topics, non-trial research types, articles published before 2017, and articles not published in peer-reviewed journals.

Study selection
Article selection is done by collecting articles obtained in a search on the database, eliminating duplicate articles, identifying article titles and abstracts that are PICOS appropriate, and reading the full text of the relevant articles manually. There were 145 articles found in the database search. Researchers identified and screened articles and obtained five complete articles that met the inclusion criteria (Figure 1).

Data extraction
The articles that have been read are then extracted in a structured manner and explored including the researchers in the article, year of publication, country, the way health education is carried out using mobile phones, research design, number of treatment samples and control samples, the control group intervention, and the effect of health education using mobile phones on hypertensive patients. Paper writing is done independently by reviewing and explaining the selected articles. The author reviews and explains the details of the article such as research objectives, methodology, findings and recommendations. Five articles were found in the full text which were subsequently designated as discussed articles because they met all the research criteria set out (Table 1).

Risk of bias
Assessment of study quality and risk of bias was performed using the Joanna Briggs Institute (JBI) critical assessment tool for this type of randomised control trial. JBI critical assessment checklist for the randomised controlled trial had 13 assessment items on the selected articles.[9]

RESULTS

The five articles analysed showed that the total number of hypertensive patients was 1,129. Hypertension patients were divided into two groups, namely the intervention group of 550 patients and the control group of 579 patients. Health education through mobile phones is carried out by sending SMS text messages, discussing in group chats, and installing special applications on the patient's mobile phone. A summary of the research results is shown in Table I.

DISCUSSION

The results showed that there was a significant positive effect of health education interventions via mobile phones on the management of hypertension in the community. Health education via mobile phones can increase patient knowledge about hypertension, improve self-management and improve the patient's ability to monitor blood pressure.[11,8] Health education interventions via mobile phones increased adherence to a low-salt diet, increased recommended physical activity, increased intake of vegetables and fruit, decreased systolic and diastolic blood pressure, and improved quality of life.[10] Health education via mobile phones can also provide patients with the latest information about controlling hypertension, antihypertensive drugs, and health services that can be utilized.[12]

Health education through mobile phones is one of the technology-based health education interventions that nurses effectively carry out in promoting health to hypertensive patients. Health education is very important to do so that patients have better knowledge about hypertension and make appropriate control efforts to avoid the risk of complications. The application of cellular-based technology in health education can increase the role of nurses to monitor the health of hypertensive patients at home, increase patient compliance with care programs, increase patient satisfaction with services, and reduce the workload of nurses as health service providers.[15] The use of mobile phones by sending SMS text messages can be a patient reminder and motivation booster for hypertensive patients to comply with the planned treatment program.[1] Health education via SMS is also effective in increasing knowledge about hypertension and healthy lifestyles in hypertensive patients who have a hearing impairment.[16] Health education using SMS is effective in promoting medication adherence to hypertensive patients.[17]

Health education using mobile phones through discussion in group chats can be an economical and efficient model for handling future hypertensive patients for the community.[8] Health education using mobile phones through discussion in the group chat or WeChat can increase patient knowledge about hypertension and self-management, and can increase the patient's ability to monitor blood pressure.[13] The use of mobile device technology or mobile phones can support self-care for hypertensive patients, especially in adherence to programmed anti-hypertensive drugs.[18] Knowledge is one of the factors that influence the health behaviour of patients with chronic diseases including hypertension in increasing adherence to disease control programs, preventing complications, and improving the quality of life.[19]

Health education through a special application installed on the patient's mobile phone is very helpful in the management of hypertension sufferers. Health education using special applications as reminders and health education on mobile phones has increased patient knowledge about

Table I: Summary of results

Researcher, Year	Country	Research Design and Number of Subjects	Actions on Patients as the Intervention Group	Action on Patients as the Control Group	Intervention Results and Their Effect on Hypertensive Patients
Jahan Y, et al.[10] (2020)	Bangladesh	Randomised controlled trial 420 hypertensive patients; 209 patients as the intervention group, 211 patients as the control group	Health education via SMS text messages	only receive direct health education without receiving health education via SMS text message	Increased adherence to a low-salt diet, increased recommended physical activity, increased intake of vegetables and fruit, decreased systolic and diastolic blood pressure, and improved quality of life.
Abu-El-Noor NI, et al.[11] (2020)	Gaza Strip, Palestine	Randomised controlled trial 191 hypertensive patients; 97 patients as the intervention group, 94 patients as the control group	Health education using reminders and education applications on the mobile phone	received no intervention from the research team and they continued with their daily routine	Increased knowledge, increased adherence to hypertension treatment
Tahkola A, et al.[12] (2020)	Finland	Randomised controlled trial 111 hypertensive patients; 57 patients as the intervention group, 54 patients as the control group	Health education via SMS text messages	was managed by the treating physician without intervention in the study	Patients get new information about hypertension control, antihypertensive drugs, and health services that can be utilised
Li X, et al.[13] (2019)	Guangzhou, China	Randomised controlled trial 253 hypertensive patients; 110 patients as the intervention group, 143 patients as the control group	Health education through group chat (WeChat)	only received the usual health care service such as direct counselling	Increased knowledge about hypertension, improved self-management, and increased ability to monitor blood pressure
Márquez Contreras E, et al.[14] (2019)	Huelva, Spain	Randomised controlled trial 154 hypertensive patients; 77 patients as the intervention group, 77 patients as the control group	Health education through applications installed on mobile phones; AlerHTA	received the usual intervention	Improvement of pharmacological medication adherence and increased adherence to blood pressure control

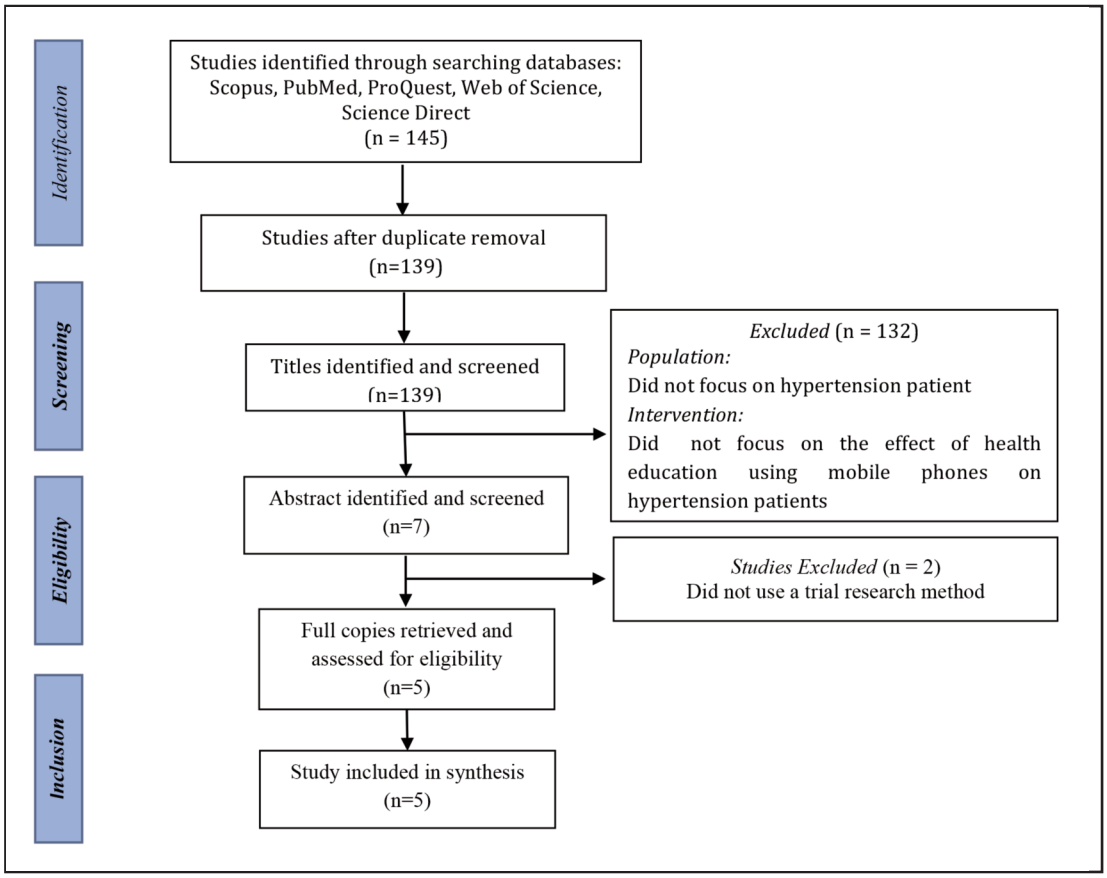

Fig. 1: PRISMA flow diagram of article selection process.

hypertension and increased adherence to treatment.[11] Health education through applications on mobile phones; AlerHTA has been able to increase patient compliance in pharmacological treatment programs and improve patient compliance in controlling blood pressure.[14] Various special applications can be installed on mobile phones for hypertensive patients to help manage nursing care. The breathing meditation exercise application via mobile phone (Tension Tamer, TT) can facilitate patients in doing breathing meditation exercises and recording the patient's heart rate or heart rate during the training session. in uncontrolled patients with stage 1 hypertension. The TT application is a promising health education choice to provide training and education to hypertensive patients at the same time.1 Digital health and fitness applications developed in cardiovascular health promotion (mHealth) with a community participation approach have also been shown to influence the lifestyle of patients who are more culturally engaged in addressing disparities in cardiovascular health problems.[20]

Although the use of mobile phones and health education applications has many benefits, nurses need to consider the patient's age to use health education via mobile phones and pay attention to the patient's socioeconomic status, literacy conditions, and ability to use mobile phones in receiving health education that will be given.[21] Hypertension patient care management can also be done comprehensively with health education, direct nursing consultation, telephone contact, home visits, and referrals. This action supports increased patient compliance in taking antihypertensive drugs that lower blood pressure and also supports a decrease in body mass index and waist circumference in hypertensive patients who are overweight.[22] Health education with the 5A model self-management program is effective in increasing the self-efficacy of hypertensive patients. One of the components in the 5A model of self-management health education is to regulate and assess the progress of self-care for hypertensive patients at home using the telephone.[23] Health education interventions by direct face-to-face individual teaching can also be a convenient option to improve hypertension patient medication adherence in a group of hypertensive patients with low socioeconomic status.[17]

STUDY LIMITATIONS

This systematic review has several limitations. One of the drawbacks is that it does not perform statistical meta-analysis of the data so that research results cannot be presented accurately in the form of statistical data. As a result, there is a possible bias towards the results of this study. We also acknowledge that the data presented are only a limited collection of data on the effects of health education through cell phones. However, this study really helped us to obtain research evidence on the magnitude of the effect of health education on hypertensive patients via mobile phones.

CONCLUSION

Health education via mobile phones has a significant positive effect on hypertensive patients. The effect of health education through mobile phones is that it can increase patient knowledge about hypertension, improve self-management, and ability to monitor blood pressure. Health education via mobile phones can improve hypertension patient compliance in pharmacological treatment programs, adherence to a hypertensive diet such as low salt, increased intake of vegetables and fruit, increased recommended physical activity, decreased systolic and diastolic blood pressure, and improved quality of life. Health education via mobile phones can also provide patients with the latest information quickly about controlling hypertension, antihypertensive drugs, and health services that can be utilised.

CONFLICT OF INTEREST

The authors declare that there no conflict of interest regarding the publication of this paper.

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A pre-admission triaging tool to predict severe COVID-19 cases: ABCD score

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SUMMARY

Introduction: Isolation of SARS-CoV-2-infected individuals is an important COVID-19 pandemic control measure. While most cases have uncomplicated infection, a small proportion of them has developed life-threatening disease. We set up a retrospective study to determine preadmission triaging tool to predict the development of severe COVID-19.

Materials and Methods: A retrospective study was conducted from 1 October 2020 to 31 January 2021 with enrolment of all SARS-CoV-2 PCR-confirmed persons aged ≥13 years. The disease severity was assessed on admission and daily throughout the hospitalisation. Test-positive individuals were considered as having "severe COVID-19" if they had ≥1 of the following: room air oxygen saturation 30 breaths/minute, signs of severe respiratory distress, or received mechanical ventilation and/or vasopressor therapy. Uni- and multi-variate analyses using SPSS Statistics Ver. 26 were performed.

Results: We showed that age ≥ 60 years, BMI ≥ 30.0, presentation on days 7–12 of illness, and ≥1 comorbidity were associated with development of severe COVID-19. A scoring system based on the four variables is a useful COVID-19 risk assessment tool. A total score ≥2 had a sensitivity of 60.9%, specificity of 88.2%, positive predictive value of 37.8% and negative predictive value of 95.0%.

Conclusion: Development of preadmission triaging tool can help health care providers (HCPs) decide on the placement of test-positive individuals to appropriate isolation facilities according to the risk of developing severe COVID-19.

KEYWORDS:
COVID-19, Sarawak, preadmission, risk stratification, ABCD score, triage, severe

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection caused by SARS CoV-2 virus has a broad spectrum of clinical presentation that ranges from asymptomatic infection, mild undifferentiated viral illness to life-threatening disease.[1,2] While majority experience a self-limiting illness, a significant minority progress to develop severe disease. These individuals may experience fulminant cytokine storm or multi-organ failure with resultant death.[3] Isolation of test-positive individuals is a key public health measure in controlling virus transmission and protecting vulnerable individuals from this potentially lethal infection.[4] Public health authorities were compelled to isolate test-positive individuals at minimally equipped makeshift isolation facilities, such as hotels, hostels, and community halls due to limitation in number of hospitals beds. This may result in suboptimal monitoring and delayed treatment. This highlights the importance of case triage to identify individuals who may progress to severe illness so that they can be cared at appropriate facilities. This is particularly important as health care facilities were already inundated with critically ill COVID-19 cases.[5] The channelling of appropriate resources to look after these high-risk individuals is crucial in a resource-limited setting. Several COVID-19 risk prediction models have been proposed since the early days of the pandemic to identify at-risk individuals. However, most models include specific laboratory and radiological details.[6,7] We set up a retrospective study with the aim to determine clinical variables associated with the development of severe COVID-19.

MATERIALS AND METHODS

A retrospective chart review (Malaysian Medical Research Ethics Committee NMRR-20-1656-55896) was conducted at Sarawak General Hospital and its affiliated makeshift isolation facilities from 1 October 2020 to 31 January 2021. All SARS-CoV-2 PCR-confirmed persons aged ≥13 years were enrolled. We excluded paediatric cases in this study. All data were collected using standardised data collection form and being anonymised for the analysis.

We assessed the disease severity of each test-positive individuals on admission and daily throughout the hospitalisation. Individuals were classified as severe COVID-19 infection if they had any of the following: room air oxygen saturation < 90%, respiratory rate > 30 breaths/minute, signs of severe respiratory distress, or received mechanical ventilation and/or vasopressor therapy.[8] Subjects without above features were classified as non-severe COVID-19.

Uni- and multi-variate analyses (SPSS Statistics Ver. 26) were used to determine clinical variables associated with the development of severe disease. A scoring system was generated by assigning point scores to each identified variable based on the coefficient in logistic regression. The

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Table I: Clinical characteristics of COVID-19 cases admitted to Sarawak General Hospital and its affiliated isolation facilities from 1st October 2020 to 31st January 2021

Clinical parameters	Total (n=607) n (%)	Severe disease (n=64)	Non-severe disease (n=543)	Univariate analysis, p	Multivariate analysis, P, OR (95% CI), Co-efficient
Male	326 (53.8%)	30 (47.6%)	296 (54.5%)	0.299	-
≥ 60-year-old	80 (13.2%)	33 (51.6%)	47 (8.7%)	<0.001	<0.001, 11.8 * (6.4-21.7), 2.3
BMI ≥ 30	110 (18.1%)	23 (35.9%)	87 (16.0%)	<0.001	<0.001, 3.5 ** (1.8-6.7), 1.2
Comorbidities					
Comorbid (Any)	58 (9.6%)	13 (20.3%)	45 (8.3%)	0.002	0.025 *** - 0.8
• Ischemic heart disease	16 (2.6%)	8 (12.5%)	8 (1.5%)	<0.001	-
• Diabetes mellitus	34 (5.6%)	4 (6.3%)	30 (5.5%)	0.811	-
• Chronic kidney disease	1 (0.2%)	0	1 (0.2%)	0.731	-
• Malignancy	5 (0.8%)	1 (1.6%)	4 (0.7%)	0.489	-
• Bronchial asthma	9 (1.5%)	2 (3.1%)	7 (1.3%)	0.250	-
• COPD	1 (0.2%)	0	1 (0.2%)	0.799	-
Day 7 to 12 of illness	89 (14.7%)	17 (26.6%)	72 (13.3%)	0.004	0.016, 2.2 (1.1-4.5) ****, 0.8
Symptoms					
Symptomatic	317 (52.3%)	30 (46.9%)	287 (52.9%)	0.365	-
• Fever	170 (28.1%)	25 (39.1%)	145 (26.8%)	0.038	-
• Rhinorrhoea	82 (13.5%)	10 (15.6%)	72 (13.3%)	0.605	-
• Cough	178 (29.4%)	33 (53.1%)	145 (26.6%)	<0.001	-
• Dyspnoea	24 (4.0%)	13 (20.3%)	11 (2.0%)	<0.001	-
• Vomiting	3 (0.5%)	0	3 (0.5%)	0.658	-
• Diarrhoea	29 (4.8%)	4 (10.8%)	25 (4.4%)	0.076	-
Blood investigations					
• Haemoglobin (g/dL)	14.3 (13.2-15.5)	13.7 (12.4-14.7)	14.4 (13.3-15.6)	<0.001	-
• Total white cells (10^3/uL)	6.4 (5.1-8.1)	6.0 (4.4-7.5)	6.4 (5.2-8.1)	0.031	-
• Lymphocytes (10^3/uL)	2.0 1.5-2.6)	1.4 (1.1-1.9)	2.1 (1.6-2.6)	<0.001	-
• LDH (U/L)	346.5 (369.1-418.0)	435.5 (351.2-581.0)	338.0 (268.5-409.0)	<0.001	-
Outcome					
Mortality	4 (0.7%)	4 (0.7%)	0	-	-

The Mann-Whitney U test was used for numerical variables and either the $\chi 2$ test or Fisher exact test was used for categorical variables.
* Reference group: age < 60-year-old
** Reference group: BMI < 30
*** Reference group: No comorbidity
**** Reference group: Asymptomatic or any other day of illness other than day 7 to 12

Table II: The distribution of the total score of the 607 COVID-19 cases according to the disease severity on admission and subsequent development of severe COVID-19.

Disease severity group	Disease severity on admission and subsequent progression	N (%)	Median (IQR)	0	1	2	3	4
Severe COVID-19	1. Severe disease at presentation	5 (0.8%)	1.4 (0.5-2.0)	1 (20.0%)	1 (20.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)
	2. Non-severe disease on admission, developed severe COVID-19 during the isolation period	36 (5.9%)	1.3 (1.0-2.0)	4 (11.1%)	19 (52.8%)	10 (27.8%)	3 (8.3%)	0 (0.0%)
Non-severe COVID-19	3. Remained to have non-severe disease throughout the isolation period	566 (93.2%)	0.5 (0.0 -1.0)	337 (59.5%)	181 (32.0%)	43 (7.6%)	4 (0.7%)	1 (0.2%)

Table III: Diagnostic performance of the scoring system based on age, body mass index, day of illness and the presence of co-morbidity*

Total score	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	+LR
1 and above	89.0 (78.7-95.4)	61.6 (57.4- 65.8)	21.5 (19.2-23.9)	97.9 (95.9-98.9)	2.3
2 and above	60.9 (47.9-72.9)	88.2 (85.2-90.8)	37.8 (31.0-45.1)	95.0 (93.3-96.3)	5.1
3 and above	32.8 (21.5-45.6)	96.1 (94.1-97.5)	50.0 (36.6-63.3)	92.3 (91.0-93.5)	8.4
4 and above	4.6 (21.5-45.6)	99.2 (98.1-99.8)	42.8 (14.6-76.6)	89.8 (89.3-90.3)	6.3
5	0.0 (0.0-5.6)	99.8 (98.9-100.0)	0.0	89.4 (89.4-89.4)	0.0

* Age ≥60 years was assigned with two points, and BMI ≥30, presented on day 7-12 of illness and ≥1 co-morbidity each with one point.

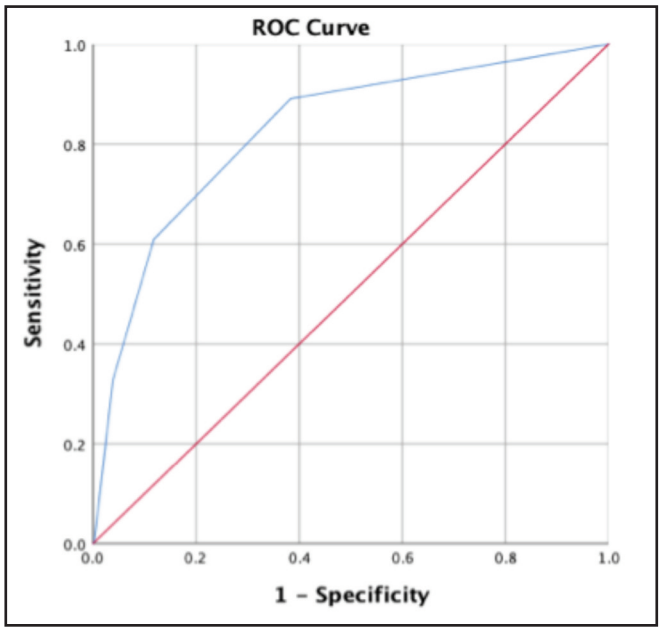

Fig. 1: The Receiving Operating Characteristic (ROC) curve of the ABCD score.

total score was calculated for each test-positive individual, and the diagnostic performance of the scoring system in identifying test-positive individuals who developed severe COVID-19 was examined by receiver operating characteristic (ROC) curve.

RESULTS

Six-hundred and seven test-positive individuals were recruited of which 5.4% had severe disease on admission. Of the remaining individuals, another 5.4% developed severe COVID-19 subsequently. We compared clinical variables of individuals who had either severe COVID-19 on admission or thereafter (N = 64) with those who had non-severe COVID-19 (Table I). Significantly more cases with background of ischemic heart disease (IHD) developed severe COVID-19. Significantly more cases in severe COVID-19 group had cough and dyspnoea.

Factors such as age ≥ 60 years, body mass index (BMI), the presence of ≥1 comorbidities, and presentation on days 7–12 of illness were significantly associated with severe diseases on univariate analysis. Based on coefficient in logistic regression, we assigned age ≥ 60 years (A) with two points, and BMI ≥ 30 (B), ≥1 comorbidity (C), and presentation on days 7–12 of illness (D) each with one point. The total score of every individual was recorded based on assessment upon admission.

Individuals who had severe COVID-19 were more likely to have a total score of ≥2 compared with those who had non-severe COVID-19 [16/41 (39.0%) vs. 48/566 (8.5%), $p < 0.001$] (Table II). Total score ≥2 had a sensitivity of 60.9%, specificity of 88.2%, positive predictive value of 37.8% and negative predictive value of 95.0%. (Table III). The area under the curve of ROC curve was 0.82 (95% CI: 0.77–0.88, $p < 0.001$) (Figure 1).

DISCUSSION

We demonstrated that ABCD score could be used to identify individuals who are likely to have severe COVID-19 disease. The scoring system can be applied with minimal clinical variables, even from phone consultation. This enables HCP to perform immediate risk assessment and triaging to identify high-risk individuals to be placed in facilities equipped for close observation. Cases who had disease progression in makeshift isolation facilities usually brought detrimental outcomes. Several COVID-19 risk prediction models have been proposed to aid clinicians assess the likelihood of severe disease when faced with SARS-CoV-2-infected individuals.[6,7,9,10] The existing risk prediction models were based on severe COVID-19 cases who were admitted to intensive care units.[9,10] Most models require specific laboratory and radiological features that involve blood sample collection and diagnostic imaging that may not be readily accessible in all clinical settings with a short turn-around time.

The limitation of our study is that the variables were identified through a small cohort over a short study period and have not been validated with a larger cohort in a prospective manner. Prospective study with larger cohort can be considered to validate this scoring system.

CONCLUSION

We developed this ABCD scoring system with four easy-to-elicit clinical variables that can guide HCP decide placement of test-positive individuals to appropriate isolation facilities according to the risk of developing severe COVID-19.

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CONFLICT OF INTEREST

None to declare.

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Brain tumour in adolescents and young adults: Challenges in making the diagnosis for frontliners

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Dear editors,

Brain tumours in adolescents and young adults (AYA) often pose diagnostic challenges due to their various features of presentation. Since headache is the most common complaint for this condition, there is some overlap between primary headache syndromes. The standard age ranges from 15 to 39 years in AYA patients, making primary headache syndrome the most prevalent diagnosis. Thus, a prolonged period of misdiagnosis is not uncommon. Local data show that brain tumours are common in those more than 40 years old and peak between 51 and 60 years of age.[1] However, our data show that those who have had a headache for more than one month would have multiple outpatient visits before being diagnosed.

We share two cases illustrating challenges in diagnosing brain tumour in AYA patients. The first case involves a 24-year-old lady, an engineering student who had daily headaches for one year. The location of the headache was at the occipital region, and the headache was throbbing in nature and progressively worsening over the past year. She had visited multiple outpatient visits for the past year and was treated with paracetamol. She also complained of bilateral blurring of vision and photophobia for the past four months, which was not corrected by wearing spectacles. The symptoms were associated with occasional vomiting, loss of appetite, and unintentional weight loss of approximately 7 kg in four months. Clinically, she was alert and orientated to time, place, and person. Her vital signs were stable. Upon examination of the cranial nerves, she was found to have anosmia and impaired visual acuity (right side 6/12 and left side 6/15). Her pupils were 3-mm in diameter, bilateral, and reactive. Otherwise, her motor, sensory, and cerebellar examinations were normal. Her plain computed tomography (CT) of the brain showed the presence of an intraparenchymal lesion at the frontal lobe compressing the ventricles. Magnetic resonance imaging (MRI) T2W showed a heterogeneously hyperintense mass with avid enhancement noted in the postcontrast study. She was admitted to the neurosurgical ward and underwent surgery.

The second case involves a 21-year-old lady who presented to an outpatient with blurred vision in the left eye for one week. She was concerned about her visual impairment as she failed her driving tests. Upon fundoscopy examination at the clinic, she was found to have bilateral papilledema and was referred to the ophthalmology clinic for a detailed eye assessment. Further history revealed that she had an intermittent right-sided headache associated with nausea and vomiting for four years. For the past year, she started to feel occasional right-sided facial numbness and anosmia. She had had multiple outpatient visits previously for her headache and was treated symptomatically. She also had a history of low mood and forgetfulness. Her visual acuity was 6/6 over the right eye and 6/24 over the left eye. She was diagnosed with bilateral papilledema. Her pupils were 3-mm in diameter, reactive, and bilateral. Upon examination by the neurosurgical team, the patient had impaired olfaction and vision, with altered sensation over the left-sided trigeminal nerve distribution. The corneal reflex was impaired over the left eye. The findings of motor, sensory, and cerebellar system examination were normal. Her CT of the brain showed a large lobulated extra-axial mass centred in the anterior cranial fossa with a connection to the falx. Brain MRI showed an extra-axial anterior midline mass, likely intraventricular in origin. She underwent bifrontal craniotomy and tumour excision.

Both cases illustrated the absence of limb weakness during the presentation. Instead, these cases had neuro-ophthalmic complaints such as headaches and blurring of vision in addition to anosmia. Complete cranial nerve examinations are paramount to avoid missing the diagnosis. Fundoscopy is necessary, and the ability to detect early stage of papilledema is essential. The MOBI-Kids study showed that neurological deficits occur in only 40% of cases[2] and may be a late feature. Therefore, a lack of motor and sensory deficits does not rule out a brain tumour. The locations of the brain tumours determine the clinical features. The most common tumour site in AYA patients is the frontal lobe (28.8%), followed by the temporal lobe (13%), cerebellum (8.7%), parietal lobe (7%), brainstem (6%), occipital lobe (1.4%), and the remaining parts of the brain (35.1%). Symptoms such as visual abnormalities, behavioural changes, and cognitive and memory impairment should be taken seriously during history taking.[2]

Although a mnemonic of SNOOP for red flag features was emphasised for better detection of sinister secondary headache, the focus is mainly for those more than 40 years. SNOOP stands for systemic symptoms or signs, neurologic symptoms or signs, sudden onset or onset after the age of 40 years, and changing headache patterns.[3] Therefore, there are limitations in applying these red flag features for screening AYA patients.

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A high index of suspicion is critical at the primary care level and emergency department to diagnose brain tumours in AYA patients. Many patients went on to have multiple outpatient visits before receiving appropriate diagnostic imaging. The non-specific early symptoms of brain tumours, such as anosmia and neuro-ophthalmic complaints, should be followed by a thorough neurological examination. Early detection and management are crucial, as most brain tumours in AYA patients have good prognoses.

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Parotid tuberculosis in an immunodeficient patient: A rare case not to be missed

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SUMMARY

Extrapulmonary tuberculosis (TB) poses challenges due to its diverse clinical presentation and the complex diagnosis pathway. It includes parotid TB, which has always been underdiagnosed, mismanaged, delayed treatment initiation, and being among the last diagnosis to be made due to the low level of suspicion. Despite living in an endemic area of TB, it is still uncommon for a primary care doctor to propose the diagnosis at the beginning. Therefore, a late diagnosis would lead to an unforeseen circumstance, especially in an immunodeficient state patient. We report a case of a human immunodeficiency virus (HIV) with a parotid swelling mimicking a cancerous lesion at the initial stage and later showing signs of inflammation. Anti-tuberculous treatment was initiated, improvement was seen, and he had successfully completed 12 months of treatment.

INTRODUCTION

Ten million people were reported to have contracted tuberculosis (TB) in 2019 globally, with nearly 1.3 million deaths, making TB the number one infectious killer worldwide. An immunosuppressive state such as HIV contributes to TB mortality, with people living with HIV dying due to TB at 208,000 cases in 2019. Both TB and HIV have a synergistic effect on each other. TB will increase HIV replication and viral heterogeneity; meanwhile, HIV lowers immunity. Hence, predispose hosts to TB infection.[1] Extrapulmonary TB infection is considered stage 4 HIV although TB infection can occur at any stage of HIV progression. Co-infection of TB in people living with HIV can make them 20 times more likely to be ill and three times at risk of succumbing to death than those without. They also tend to have extrapulmonary TB and smear-negative pulmonary TB. A retrospective study from TB national surveillance data from 2014 to 2017 found that about 19.3% had unsuccessful treatment and revealed that extrapulmonary TB and pre-existing illnesses such as HIV are essential critical factors for failed treatment.[2] Thus, a late diagnosis of tuberculous infection in this susceptible community should be avoided.

Parotid TB remained a neglected diagnosis infrequently reported even in endemic regions like Malaysia. As a result, it is rarely encountered and constitutes only 2.5% to 10% of salivary gland TB.[3] However, it is commonly seen in endemic regions such as the African and Asian continents, affecting all ages and gender groups. Clinically, the case presentation always imitates a parotid tumour. Unfortunately, although it is a treatable disease with only anti-tuberculous medication required, most cases undergo unnecessary surgical intervention.[4] Such a dilemma could be avoided if the disease could be detected early. We present a rare case of parotid TB in an immunodeficient patient who presented to our clinic with neck swelling.

CASE REPORT

A young gentleman aged 38, who was a known case of the retroviral disease since 2013, and recently started on antiretroviral therapy for three months prior to the onset of illness with a CD4 count of 470 presented to our clinic with neck swelling. The painless swelling was located at the left parotid region and progressively enlarged over three months. There were also multiple other lateral neck swellings that appeared over this course of time. He also experienced fever on and off for the past few months, with each episode lasting for two to three days. He received three courses of antibiotics throughout the illness, in which he developed loose stool after antibiotic initiation. However, no improvement was seen. He denied any previous history of TB, obstructive symptoms, prolonged cough, night sweat, constitutional symptoms, contact with any tuberculous pulmonary patient, or facial asymmetry. The physical assessment revealed a non-erythematous parotid swelling measuring 4 × 1 cm, minimally tender on palpation, with a centrally fluctuant area felt (Figures 1 and 2), and also the presence of an ipsilateral enlarged cervical lymph nodes at the level of I, III, and IV. All the swollen nodes were firm in consistency, mobile, non-tender, and not erythematous, measuring around 1 × 1 cm each.

Meanwhile, his facial nerve was intact, as well as his other examination. He was then referred to the otorhinolaryngology specialist clinic with the impression of parotid abscesses to rule out malignancy. He was treated as parotid abscesses in the specialised clinic, and he was then discharged with antibiotics and planned for an ultrasound neck. Ultrasound neck showed a hypodensity area in the parotid region. A chest X-ray was performed and revealed normal lung findings. Later, he presented again with the complaint of discharging pus from the parotid swelling. Proceeded with incision and drainage on the same day, a sample of pus for acid-fast bacilli was sent. A positive result was revealed. Hence, an anti-tuberculous regime was initiated. He responded well to the chemotherapy.

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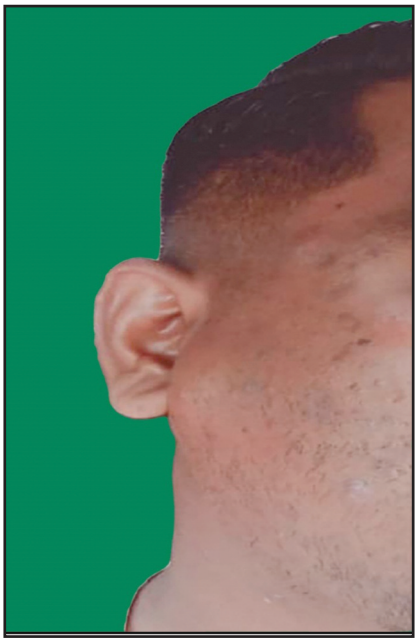

Fig. 1: Left parotid swelling (front view).

Fig. 2: Left parotid swelling (side view).

DISCUSSION

In Malaysia, TB is still endemic, with 92 per 100,000 population in 2019. However, a case of parotid TB remains a rare entity to be reported. There were less than 300 reported cases since it was first detected in 1894, and various presentations have been observed.[5] Therefore, it is more challenging for primary care physicians to make early diagnoses. The differential diagnoses for chronic parotid swelling are malignancy, HIV parotitis, amyloidosis, sarcoidosis, sialadenitis, Sjogren's, or polyangiitis granulomatosis. In addition, any factor contributing to TB is also a risk for contracting parotid TB, such as low socioeconomic levels, promiscuity, TB infection, and immunodeficient conditions like this patient.

Generally it presents as an indolent painless parotid swelling mimicking a cancerous swelling, like this case at its initial stage, it is also not uncommon to have an acute infectious state that appeared later in this case. Some authors reported that it could present as a recurrent discharging parotid swelling along with systemic symptoms. In cases with discharging parotid TB, features to suggest infection such as erythema, swelling, and pain are absent. Meanwhile, there are cases with asymptomatic unilateral preauricular swelling that has been observed.[6] Most of them are unilateral parotid swelling; however, bilateral involvement also has been noticed in this disease. Patients with parotid TB can either have coexistence of enlarged cervical lymph nodes or not. The presence of cervical adenopathy with painless parotid swelling, like this case in its initial stage, may confuse the treating physician with parotid malignancy. In addition, the presence of facial nerve paralysis will favour a diagnosis of parotid malignancy, which is not apparent in this case. Meanwhile, co-infected pulmonary and parotid TB has been encountered in quite a few cases. Unlike pulmonary TB, the presence of night sweat, weight loss, and fever are rarely present. The coexistence of pulmonary TB symptoms will guide the general practitioner to diagnose parotid TB earlier, however this was not the case in this patient. Thus, it contributed to the delay in making the diagnosis.

The difficulty in diagnosing parotid TB from the preliminary assessment and in being able to differentiate it from malignancy makes ultrasound the first diagnostic tool to be done. Since ultrasound is an operator dependence imaging, most parotid TB cannot be picked up.[4] Furthermore, most of the lesions showed features of malignancy in ultrasound. Thus, it leads to surgical resection in most cases. One study found that a positive Mantoux test with cervical adenopathy, together with a suggestive lesion found in computerized tomography (CT) or magnetic resonance imaging (MRI), may be helpful to make a diagnosis of parotid TB. We can conclude that with the limited diagnostic radiological modalities, late diagnosis has always been encountered.[5] Thus, ultrasound-guided fine needle aspiration cytology (FNAC) is recommended as the gold standard diagnostic tool, subsequently avoiding unnecessary surgical intervention. As of treatment, a 9–12-month anti-tuberculous treatment will significantly settle the infection.

CONCLUSION

A high index of the possibility of parotid TB is required when dealing with people living with HIV. On top of that, a chronic parotid swelling that is resistant to multiple attempts of antibiotic course should alert the attending physician of parotid TB, particularly in endemic countries. Due to its varied presentation and difficulty to choose the best preliminary test, perhaps the aid of the Mantoux test and suggestive features of parotitis in ultrasound could be an appropriate initial step for primary care physicians.

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CONFLICT OF INTEREST

None to declare.

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CASE REPORT

Not all wheeze is asthma: A case of central airway foreign body mimicking asthma

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SUMMARY

Foreign body aspirations are more commonly seen in the paediatric age as compared to adults. This is more widely seen in the older population due to the impairment of protective airway mechanisms or the absence of the swallowing reflex, for instance, in neurological diseases, head trauma, alcohol intoxication, sedation, or complications from dental manipulation. We report the case of a betel nut causing airway obstruction in an elderly lady, which was treated multiple times as respiratory tract infection and asthma. Subsequently, a bronchoscopy was performed. Following which, the betel nut was removed causing resolution of symptoms.

INTRODUCTION

Foreign body aspiration is a rare occurrence in adults.[1-5] Patients usually present with subacute symptoms namely cough, wheeze, shortness of breath, and haemoptysis.[1,2,4-7] They are often misdiagnosed as having a common cold, pneumonia, or asthma refractory to inhalers. Interventions include flexible bronchoscopy, rigid bronchoscopy, and removal via thoracotomy.[2,7,8] The more popular approach is through flexible bronchoscopy, as it was found to be very effective according to some studies. In one such study, Sehgal et al. had found that 65 out of 25,998 flexible bronchoscopies they reviewed were done to remove foreign bodies; their success rate was almost 90%.[1]

CASE REPORT

We report the case of a 65-year-old lady, who has no known medical illnesses. She complained of a chronic cough of more than 2 months duration, which was non-productive and with no diurnal variation. She initially had a fever 2 months ago, which resolved within a few days. Subsequently, she started to develop wheeze, shortness of breath, loss of appetite, and a 4-kg weight loss in 1-month duration. However, she did not experience night sweats, haemoptysis, or any recent exposure to pulmonary tuberculosis patients. She had visited a few clinics and completed multiple courses of antibiotics over the past couple of months; however, the cough persisted. Subsequently, she was started on inhaled corticosteroids and a diagnosis of late-onset bronchial asthma was made. She was tested negative for tuberculosis and was seen in a local health clinic. She was referred to our centre due to recurrence of symptoms and no clinical improvement for further management. Upon reviewing her in the respiratory clinic, she was not tachypnoeic and oxygen saturation was 100% under room air, although it was noted that she had an audible stridor. Lung auscultation revealed inspiratory rhonchi. The chest radiograph was normal (Figure 1a). A spirometry showed features suggestive of variable extra-thoracic obstruction (Figure 1b). Although her spirometry technique was not correct, that was the best she could perform, and flattening/limitation of the inspiratory limb was noted in the spirometry. She underwent flexible bronchoscopy (Olympus BF Type 1T180) under conscious sedation immediately via oral approach and a foreign body was identified at the subglottic area (Figure 2), which was promptly removed using an extraction basket (Vedkang). A betel nut was identified to be causing the obstruction. Her symptoms resolved post bronchoscopy. She was discharged and remained well when seen in the respiratory clinic 1 month later for a follow-up consultation.

DISCUSSION

Betel nut or areca nut chewing is a time-honoured custom in Southeast Asia, and it presents a rare complication of being aspirated into the airways, especially in healthy adults. As a result, clinicians do not diagnose it early. Such cases are often misdiagnosed, delaying appropriate management especially if there is no prior history of choking.

It is necessary to elicit a detailed history of presenting symptoms and to perform a full examination to evaluate causes of wheezing, especially in elderly patients. For most patients, the initial evaluation will include ECG, spirometry, and a chest radiograph. A clinician should be able to differentiate between wheeze and stridor. A wheeze is a continuous musical sound that is by the oscillation of opposing walls of an airway that is narrowed. Wheezes are usually high pitched, consist of single or multiple notes, and occur during inspiration or expiration (more commonly expiration). Stridor refers to a monophonic sound that is loudest over the anterior neck and is typically high-pitched and predominantly inspiratory. These steps will help the clinician to narrow down the possibilities. If symptoms persist despite initial evaluation or treatment, primary care physicians should refer the patients to a pulmonologist for further management.

This patient presented with recurrent respiratory infections and asthma-like symptoms for more than 2 months before being diagnosed with an airway obstruction. Many patients who have been managed or treated as asthma in primary care did not have baseline spirometry.[9] This point has been

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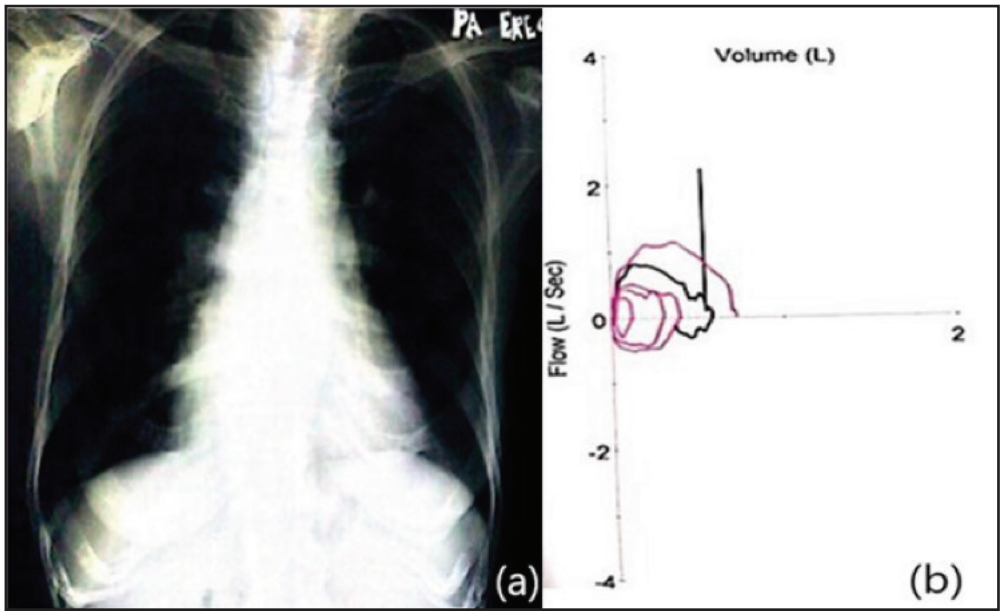

Fig. 1: Respiratory system investigations. (a) Chest radiograph showing over penetration and no evidence of atelectasis (b) Lung function test observing features suggestive of variable extra-thoracic obstruction.

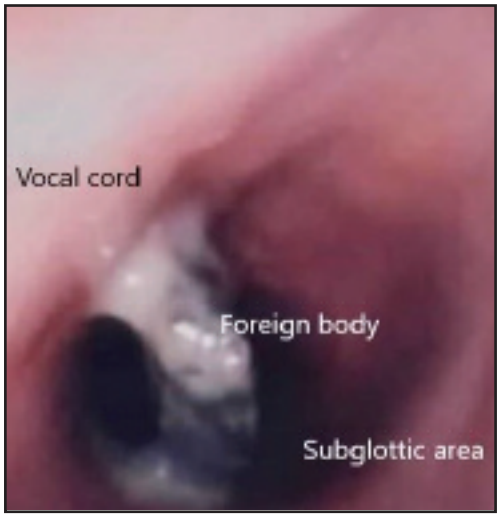

Fig. 2: Bronchoscopic image showing of the foreign body.

asserted in the ASCOPE study published in the year 2020 and in line with previous reports.[9] The possible causes are shortage of access to spirometry[9] and also COVID-19 pandemic restrictions.

Foreign body aspirations can present with symptoms such as cough, dyspnoea, wheeze, and haemoptysis.[1,2,4-7] Patients may not recall an aspiration event, especially adults. Commonly aspirated foreign bodies are food particles and broken fragments of teeth. In up to 80-90% of cases, radiolucent objects may not be detected on chest radiographs, such as food and plastic particles.[4,7] In these instances, a chest CT will be required.[6,10] The sensitivity of a multidetector CT to detect a foreign body is almost 100%, with a specificity of 66.7-100%, according to a study by Gordon et al.[10]

The complications of a chronically retained foreign body include recurrent pneumonia, lung abscess, bronchiectasis, haemoptysis, and the development of inflammatory polyps at the site of impaction.[1,4-6,8] The most common location for a foreign body to be embedded is within the right bronchial tree, due to the vertical orientation of the right main bronchus and larger diameter in comparison to the left main bronchus.[1,3-7]

In this case, the preferred instrument used to retrieve the foreign body was the flexible bronchoscopy, which was developed in 1968 by Shigeto Ikeda,[3,4] and has now become the gold standard means for localization and retrieval of an airway foreign body. This method has revolutionized the field of bronchoscopy and is significantly more advantageous as it can be manoeuvered into the distal bronchus to retrieve smaller objects safely.[1,2,3,6] It is also the more favourable method used in patients with cervical instability or facial trauma.[2,3] Usually, a flexible bronchoscope with an outer diameter 6.0-6.1 mm and an inner diameter of 2.8 mm will be used. These bronchoscopes will have a 120° field of view with angulations of 180/130 degrees. Unlike rigid bronchoscopy, it does not require the utilization of general anaesthesia making it an outpatient procedure that is costly and time-efficient.[1,4,8] In addition to that, a mechanically ventilated patient would be able to benefit from this procedure, as it allows the removal of the foreign body without the need for extubation. Bronchoscopy for foreign body removal requires proper instruments for its safe retrieval such as forceps (V-Shaped grasping forceps, rat tooth grasping forceps), baskets (mini grasping basket or grasping basket, fishnet basket) or cryoprobe.

In a study that compared flexible and rigid bronchoscopies, it was shown that flexible bronchoscopy was associated with lower mortality and morbidity in contrast to rigid bronchoscopy (1% vs 12%, respectively) as general

anaesthesia was avoided.[1] However, in cases of complex foreign bodies that were unable to be removed by flexible bronchoscopy or if flexible bronchoscopy failed immediately causing massive airway obstruction, rigid bronchoscopy would be the preferred choice.[1,3,4,6,7]

CONCLUSION

Due to its non-specific nature, adult foreign body aspirations are often misdiagnosed as an obstructive airway disease and consumes months, if not years, to identify and treat accordingly, as in the case of the elderly lady that we have presented. A high index of suspicion is needed by clinicians to reappraise the diagnosis of bronchial asthma and further investigate recurrent respiratory infections. Flexible bronchoscopy is the preferred method as it is both diagnostic and therapeutic in the aspect of foreign body removal from airways in adults, with a high success rate and low risk of complications in the hands of a skilled operator.

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CONFLICT OF INTEREST DECLARATION

The authors declare no potential conflict of interest with respect to the authorship and publication of this article.

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A case of salivary gland choristoma presenting with ear discharge in a child having external auditory canal stenosis

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SUMMARY

Salivary gland choristoma in the middle ear or external ear canal is rare. Generally, it is difficult to differentiate salivary gland choristoma from congenital cholesteatoma or cholesterol granuloma on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). It is challenging to diagnose preoperatively without specific clinical or radiological symptoms or signs. Thus, histopathological examination is required for a definitive diagnosis, and a histopathological sample of the lesion is acquired. We discuss the imaging and histology of salivary gland choristoma with the best recommendation on the management.

INTRODUCTION

Salivary gland choristoma is a type of heterotopia, a phenomenon where normal salivary gland tissues are found in an abnormal site.[1] The common locations are the posterior lobe of the pituitary gland, the periparotid lymph nodes, the middle ear, and the lower neck.[2] A unilateral conductive hearing deficit is typically the first manifestation of choristoma, with otorrhoea and occasionally a mass in the middle ear. This lesion may be associated with deformed or absent ossicles as well as branchial arch and facial nerve abnormalities.[1] Most of the reported cases of salivary gland choristoma were in children (10 cases) and adults (38 cases). Thus, we present a unique case of salivary gland choristoma presented in an infant, its clinical presentation, and radiological findings with histopathological reports.

CASE REPORT

A one-year-old baby girl was seen in the otorhinolaryngology (ORL) clinic with the complaint of episodic right ear discharge. She was born with right microtia and external auditory canal (EAC) stenosis. She also presented with right facial nerve palsy, evidenced by slight deviation at the right angle of mouth and loss of nasolabial fold. Hearing screening with the distortion product otoacoustic emission (DPOAE) machine showed a pass result in the left ear and refer result in the right ear. During her clinic follow-up, the mother claimed that the episodic mucoid discharge from the right ear improved after using topical eardrops (ofloxacin). However, since the age of eight months, there was an off and on fluctuant swelling measuring 2 × 2 cm with erythematous skin at the right infra-auricular area. Initially, it was treated with oral antibiotics, but on the third episode, the swelling did not resolve with oral medication. Hence, aspiration of the swelling was done whereby 3 ml of pus was aspirated using a needle and syringe. On follow-up, there was fibrosis at the aspirated area with the formation of cutaneous fistula with off and on mucoid discharge. Otherwise, the mother claimed that her baby was comfortable and growing well.

Due to persistent ear discharge from the canal and fistula, the baby was referred for a high-resolution computed tomography (HRCT) of the temporal bone and MRI of the ear. The HRCT findings showed a stenotic cartilaginous part and an atretic bony part of the right external auditory canal. The impression was right ear congenital cholesteatoma with absent right stapes, dysplastic long crus of right incus, and collection at the right posteroinferior auricular region. The right and left facial nerves courses were intact; however, the right stylomastoid foramen was widened compared to the left side. The MRI showed a well-defined rounded lesion posterior to the bony part of the EAC measuring 0.76 cm anteroposterior (AP) × 1.2 cm width (W) × 0.9 cm craniocaudal (CC) (Figure 1a). Lateral to this lesion, there is a well-defined collection measuring 0.3 cm in maximum thickness. Axial view of T2 drive showed normal right facial nerve from cisternal part of cerebellopontine angle to first genu. The impression was right middle ear cholesterol granuloma with the adjacent collection and right mastoiditis. The patient underwent right cortical mastoidectomy and removal of the right posterior EAC mass via trans-mastoid approach with the excision of the right infra-auricular cutaneous fistula. Intraoperative findings showed a pearly white sac occupying the right EAC measuring 2.0 × 1.5 cm (Figure 1b), that the EAC was narrowed, and the presence of a tract connecting the fistula area to the canal and noted mucoid discharge coming out from the fistula. No keratin was seen in the mastoid cavity, whereas keratin debris was seen at the EAC. The facial nerve was unable to be identified.

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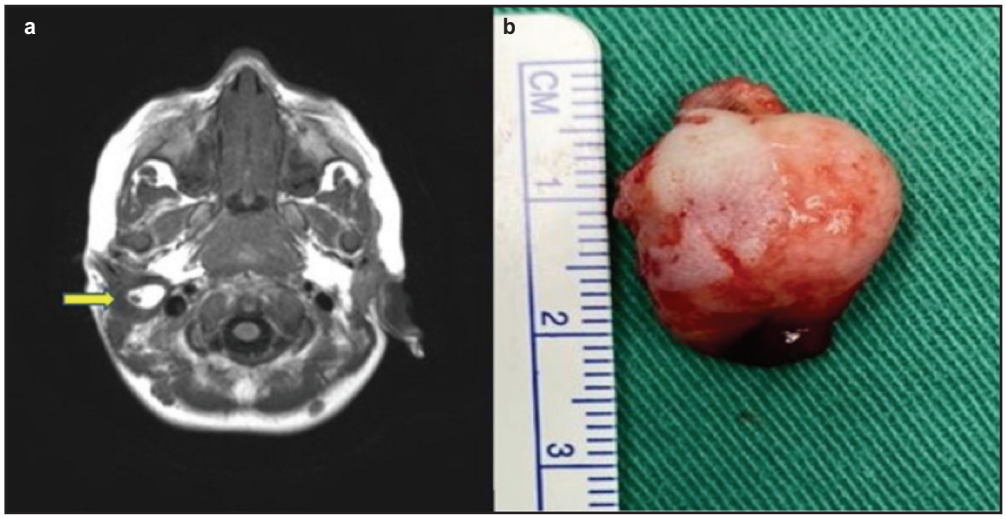

Fig. 1: Images of the choristoma. (a) MRI T1-weighted images in axial view; the arrow pointed to a well-defined rounded lesions seen posterior to the bony part of the right EAC. (b) Gross specimen of the whole sac of right auditory canal mass (pearl white sac size 2.0 × 1.5 cm) that was removed intraoperatively.

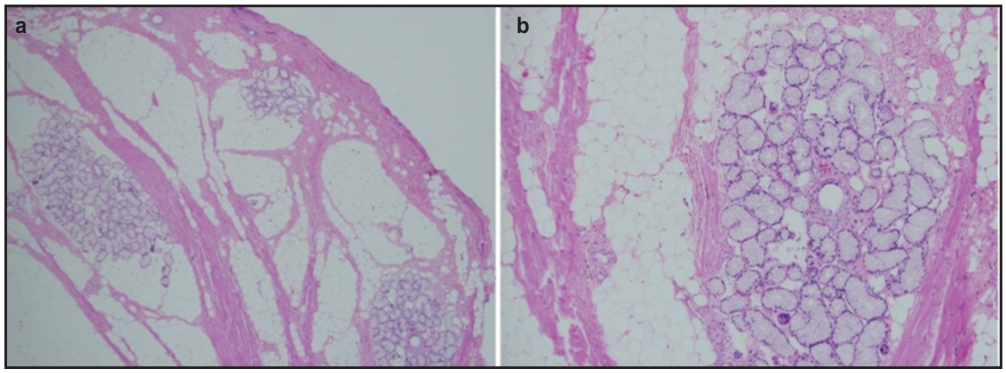

Fig. 2: Histopathological slides of the choristoma. (a) Lobules of mature adipocytes are separated by fibrous septa and scattered seromucous gland units (x10 magnification). (b) Benign seromucous gland units within the fatty tissue lobules as well as skeletal muscle bundles (x40 magnification).

The histological report stated a fairly well-circumscribed mass partly covered by stratified squamous epithelium. It is composed of lobules of mature adipocytes separated by fibrous septa. Scattered lobules of seromucous gland units were noted within the fatty tissue lobules as well as skeletal muscle bundles (Figure 2a and Figure 2b). The features were compatible with salivary gland choristoma.

DISCUSSION

The pathogenesis of the disease of choristoma is unclear. However, the choristoma occurrence is before the fourth month of gestation due to the failure of the development of the first or second branchial arch.[3] It is related to the ectopic expansion's remnant parotid epithelium or pharyngeal endoderm.[4] A few syndrome components include salivary gland choristoma, hearing loss, ossicular chain abnormalities, facial nerve anomalies, second branchial arch anomalies,[5] and other brachial arch anomalies that may also accompany the lesion.[6] The various age ranges were between 9 months and 52 years old,[7] with a ratio of two women to one man.[4]

The clinical disease feature of salivary gland choristoma occurrence in the middle ear is usually a unilateral lesion (96.8%), on which the left side was the most frequently affected (61.3%).[7] The middle ear mass must be differentiated from congenital cholesteatoma, dermoid cyst, teratoma, glomus tympanicum, granuloma, neuroma, or glioma, which are present with unilateral hearing loss without perforation of the tympanic membrane.[8] Less common areas include the upper neck, lingual mandible, external auditory canal, thyroid gland, mediastinum, prostate gland, vulva, and rectum.[2] The choristoma can be completely excised, but if it is poorly defined and intimately associated with the facial nerve, partial excision of the lesion is appropriate to prevent damage to the nerve.[1]

The extend of the excision of salivary gland choristoma is controversial. Some authors thought that salivary gland heterotopia consists of normal tissue and, thus, did not require complete excision when diagnosed histologically.[9] However, when there are signs of infection or neoplasm, it requires complete removal of the lesion.[9] The possibility of malignant transformation is very rare, but, theoretically,

choristomas are immature in nature, increasing the chance of malignancy.[10] In our case, we removed the mass with its sac and closed the fistula as a whole. It has given a better quality of life to the patient and family. There is no recurrence of ear discharge and new swelling at the operation site post-surgery.

CONCLUSION

Salivary gland choristoma of the external auditory canal is a rare benign condition and should be differentiated from other middle ear or external ear canal lesions. Infants with ear mass and recurrent otorrhea should have the salivary gland choristoma as one of the differential diagnoses. While the diagnosis of salivary gland choristoma is confirmed by histology, the best way is to remove all the lesions operatively (diagnostic and therapeutic).

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CASE REPORT

Small bowel obstruction secondary to crab shell bezoar: A case report

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SUMMARY

Small bowel obstruction is a common surgical condition that needs surgical intervention if conservative measures fail. Bezoar is a rare aetiology of small bowel obstruction with incidence of 4.5%. The bezoars can be grouped, according to the content, into four common types: phytobezoars, trichobezoars, pharmacobezoars, and lactobezoars. However, unusual bezoars like plastic bezoars and metal bezoars have been reported too. Herein, we report a case of an elderly lady who was treated for small bowel obstruction due to crab shell bezoar. This is the first case reported in literature. Ingestion of large intact pieces of crab shell should be avoided due to the potential of causing small bowel obstruction.

INTRODUCTION

Small bowel obstruction (SBO) is a common condition encountered in surgical units, of which adhesion is the most common aetiology (60%–80%).[1] Bezoar impaction causing SBO is a rare entity with a frequency of 4.5%. The definition of bezoar is an accumulation of indigestible exogenous matter in the gastrointestinal tract. Herein, we report a case of a 67-year-old lady of Asian descent who had SBO due to crab shell bezoar.

CASE REPORT

A 67-year-old lady with comorbidity of diabetes mellitus and euthyroid multinodular goitre presented with abdominal pain for a week, associated with obstipation and anorexia. Apart from abdominal distension, other physical examination was unremarkable. Her investigations revealed acute kidney injury and hyponatremia. Abdominal X-ray showed dilated small bowels.

Due to diagnostic dilemma, an urgent contrast-enhanced computed tomography (CECT) of abdomen was performed, which showed a lesion having mottled appearance and air bubbles within, measuring about 2.5 cm × 4.8 cm at the mid segment of the small bowel, causing SBO (Figure 1). The patient underwent an exploratory laparotomy, and a hard intraluminal mass at 170 cm from terminal ileum was found intraoperatively. Enterotomy was done at the mass region and revealed a few pieces of large intact crab shells forming a bezoar (Figure 2). A double barrel ileostomy was created at the site of enterotomy in view of grossly dilated proximal bowel.

After the operation, the patient admitted to ingesting crab shells one month prior to her presentation but refused to disclose the reason. Her formal psychiatric evaluation showed no abnormality. The patient's condition improved after a few days, and she was discharged from the hospital well.

DISCUSSION

Bezoars are the result of ingestion of poorly digestible or indigestible food or substance. They can be categorised, according to their content, into four common groups.[2]

1. Phytobezoars – formed by non-digestible fibres such as cellulose, hemicellulose, and fruit tannins. It can be associated with previous abdominal surgery particularly gastrectomy, bilateral truncal vagotomy plus pyloroplasty, and bariatric surgery. These surgeries cause reduced gastric motility, loss of pyloric function, and hypoacidity, which precede the formation of phytobezoar.[3]
2. Trichobezoars – formed by gastric concretion of hair fibres, usually present in patients with history of psychiatric issues and in children with mental retardation. Vaughan et al. described this condition and coined the term Rapunzel syndrome in 1968.[4]
3. Pharmacobezoars – formed by medication with tablet coating that is composed of indigestible semi-permeable cellulose acetate. Examples are cholestyramine, verapamil, nifedipine, and antacids.
4. Lactobezoars – compact mass of undigested milk concretions. It happens when highly concentrated formula is fed to low-birth-weight neonates.[5]

In addition, ingestion of unusual substances can cause formation of bezoar as well, for example, metal bezoar, plastic bezoar, and sand bezoar.6 Understanding and classifying the components of bezoars can help to tailor the management necessary for removal and prevention of recurrence.

Crabs are a type of decapod crustacean, which have an exoskeleton to protect themselves against environment and predators. The exoskeleton is made up of y α-chitin, proteins and carotenoid pigments, and an inorganic fraction where calcium carbonate is the main constituent.[7] It has been reported that crab shell ingestion can cause perforation of the oesophagus.[8]

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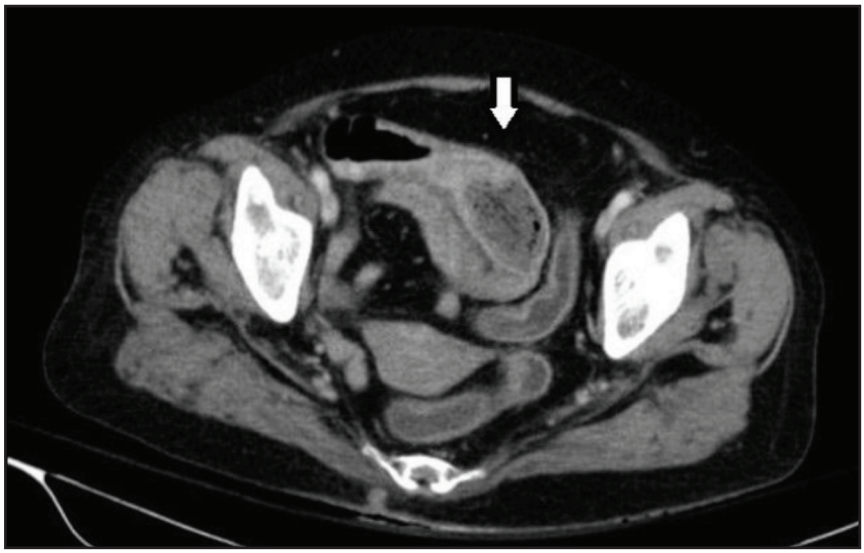

Fig. 1: Axial view of CT abdomen showing a lesion having mottled appearance and air bubbles within in the lumen of the small bowel (white arrow).

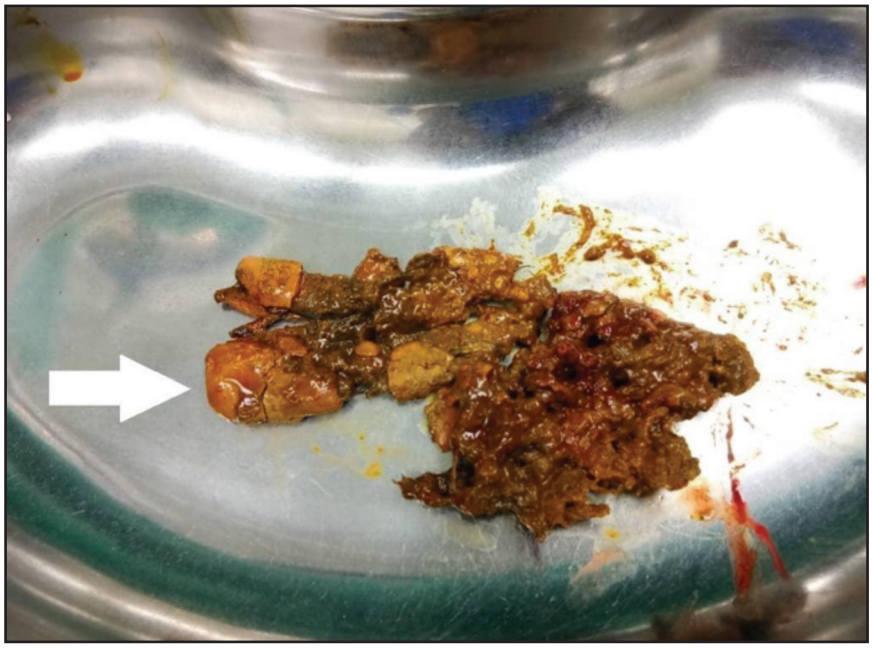

Fig. 2: Gross specimen of intra-operative crab shell bezoar (white arrow).

These bezoars are often formed in the stomach but as they undergo fragmentation, they can migrate to the small bowel and cause mechanical obstruction. Presenting features of SBO due to bezoars are often nonspecific; hence, diagnosis should be supported with imaging. Plain abdominal radiography can show signs of intestinal obstruction, but the characteristic mottled gas pattern of bezoar is only visible in 18% of cases. Barium enema is another imaging choice. It can demonstrate mobile intraluminal filling defect. Usefulness of ultrasound to diagnose bezoar is rarely described as faecal material can simulate the image of a bezoar and an intestinal tumour cannot be excluded.[9] CECT scan is the preferable choice of investigation, and its use has become more frequent. Classically, a 'small bowel faeces' sign (a mixture of particulate feculent material mixed with gas bubbles within a dilated small bowel) is suggestive of a small bowel bezoar. In a newer study, a floating fat-density debris sign (well-defined mass mottled with gas bubbles associated with an encapsulating wall) is found to be more typical of a small bowel bezoar.[10] In case of patients not suitable for CECT, non-contrasted CT can be carried out as it has higher sensitivity and specificity compared to other imaging techniques.[9]

Treatment of gastric bezoar is conservative at first, with endoscopic extraction and/or enzymatic dissolution. Extraction through gastrostomy is attempted after the above treatment fails. In contrast, small bowel bezoars are almost

always treated surgically, either milking the bezoars into the caecum or performing an enterotomy if the milking method is not possible. Laparoscopy was performed for some patients, which showed good results such as shorter operative time and shorter hospital stay, but it requires proficiency due to dilated intestinal bowels.

CONCLUSION

This is the first case of crab shell bezoar causing SBO reported in the literature. Due to the potential of oesophageal perforation and bezoar formation causing intestinal obstruction, ingestion of large intact pieces of crab shells should be avoided.

Although bezoar is a rare cause of SBO, one should always keep it in mind as one of the differential diagnoses. A thorough history taking should be taken to include previous surgery, diet history, history of taking abnormal objects, and any behavioural changes. Due to the challenges in making a clinical diagnosis, early radiological investigation with CT scan needs to be carried out so that a timely surgical treatment can be implemented.

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First documented co-infection case of cat-scratch disease and melioidosis in Malaysia: A cause of undifferentiated prolonged febrile illness

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SUMMARY

Cat-scratch disease is a zoonotic infection of worldwide prevalence that is endemic in tropical or subtropical countries. Likewise, melioidosis is one of the major endemic health problems in Malaysia. Epidemiologically, mixed infections of cat-scratch disease and melioidosis are possible because similar environmental conditions are needed for the transmission of both infections. Still, their co-infection is rarely reported in medical literature. History of contact with plantation soil or contaminated water is important in raising the suspicion of the disease. Cat-scratch disease has increased as many children are in close proximity to cats. Here, we report a case of cat-scratch disease and melioidosis co-infection in a two-year-old boy who presented with prolonged fever and painless cervical lymphadenitis and had serological testing results positive for *Bartonella henselae* and *Burkholderia pseudomallei*. A history of travelling around Malaysia during school holidays and being exposed to cat and contaminated environment are clues to diagnosis.

INTRODUCTION

Cat-scratch disease (CSD) is an emerging infectious diseases caused by the gram-negative bacteria *Bartonella henselae* and transmitted by cats. This zoonotic infection is spread by cat's saliva through direct contact with broken skin or mucosal surfaces such as an open wound or cat's bites or scratches. The disease was first described in 1931, but the causative organism was detected about 50 years later in 1983.[1] CSD is now recognised as one of the most common causes of fever of unknown origin (FUO) with unilateral lymphadenopathy.[2] Melioidosis is one of the world's most neglected tropical diseases. It is caused by *Burkholderia pseudomallei*, a gram-negative saprophyte that lives in moist soil and water in endemic areas of Southeast Asia and Northern Australia. *B. pseudomallei* was discovered in 1911 and first described as *Bacillus pseudomallei* associated with 'glanders-like' disease among morphine addicts in Myanmar.[3] This bacterium was proven to cause melioidosis in 1932 and was renamed B. pseudomallei in 1992.[3] There is no pathognomonic feature specific to melioidosis. In endemic areas, physicians need to consider melioidosis in clinical scenarios of prolonged fever, progressive pneumonia, or sepsis.

CSD and melioidosis are considered in patients with prolonged febrile illness of unclear origin.[2-5] Though co-infections of many zoonotic and tropical diseases have been described, reports on CSD and melioidosis co-infection are limited.

CASE REPORT

A two-year-old Malay boy presented with prolonged fever for three weeks. The fever was described as relapsing intermittent high grade with the highest recorded temperature of 39 degrees Celcius, but not associated with chills or rigors. Despite completing two courses of antibiotics (amoxicillin-clavulanic acid and cefuroxime), his fever persisted. He was still active during the febrile illness without other significantly associated symptoms such as cough, vomiting, or diarrhoea. There was a significant weight loss of 1.2 kg over a three-week-period. One week prior to the illness, he had history of visiting various places in Malaysia including multiple outdoor and water activities in a plantation. He also had contact with domesticated animals, particularly cats but denied being scratched or bitten by them. He had completed immunisation with no significant past medical history.

Clinically, he was active but febrile with a temperature of 39.5°C. His weight on admission was 10.7 kg at the 5th percentile for age. Physical examination was unremarkable except for a few painless palpable lymph nodes over the bilateral cervical regions with the largest lymph node measuring 2 × 2 cm in diameter. He had no hepatosplenomegaly. Preliminary blood investigations showed increased inflammatory markers; erythrocyte sedimentation rate of 105 mm/hr (reference range 0–15 mm/hr) and C-reactive protein of 5.4 mg/dL (reference range < 0.3 mg/dL) were reported.

He continued to be febrile despite empirical therapy with high dose intravenous ceftriaxone. His blood, urine and stool cultures, anti-nuclear antibody, complement proteins C3 and C4, tuberculin skin test, and chest radiographs were all negative. The *B. henselae* IgM and IgG by indirect fluorescence assay (IFA) revealed positive results with titres of 1:24 and 1:256, respectively. His serum was also positive for *B. pseudomallei* with IgM titre of 1:320. A final diagnosis of CSD and melioidosis co-infection was made.

Ultrasonography of the abdomen showed a septated right subdiaphragmatic collection measuring 2.8 × 1.1 × 3.8 cm (see Figure 1). His condition improved remarkably after the

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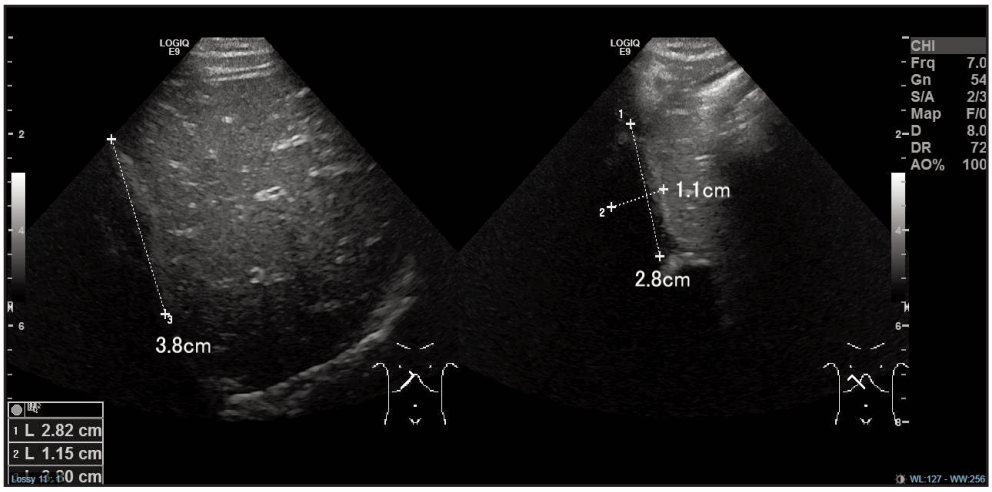

Fig. 1: Septated right subdiaphragmatic hypoechoic collection on ultrasound of the abdomen.

antibiotic treatment was changed to intravenous ceftazidime (50 mg/kg four times a day) for a total of four weeks, and completed oral azithromycin for five days (10mg/kg daily on day one then 5mg/kg daily on day two to five. He was discharged well and completed 20 weeks of oral amoxicillin-clavulanate 20 mg/kg tds at home. Unfortunately, the repeat serologies for both *B. henselae* and *B. pseudomallei* were not done at four weeks of illness due to patient/parent refusal for blood taking in view of recurrent intravenous catheter insertion.

Clinic follow-up revealed clinical improvement consistent with four-fold titre resolution; *B. henselae* IgM became negative (<1:12) and IgG decreased from 1:256 to 1:64 after two months, and *B. pseudomallei* IgM decreased from 1:320 to 1:80 within five months. A repeat abdominal ultrasonography after two months showed resolution of the right subdiaphragmatic collection.

DISCUSSION

To our knowledge, this is the first documented case of co-infection of CSD and melioidosis in Malaysia, which was confirmed by serological tests for both organisms. Clinically, symptoms of melioidosis and CSD often are nonspecific and may mimic each other.

In CSD, the typical history of being scratched, licked, and/or bitten by an infected cat may not be apparent in 25% of cases as illustrated in our patient; hence, any history of exposure is equally important.4 The infection usually begins with formation of an erythematous papule 3–10 days after exposure, followed by regional lymphadenopathy that appears 1–3 weeks post-inoculation, often non-tender, and frequently occurs in the axilla and epitrochlear (45%), head and neck (26%), and groin (17.5%) regions.[4,5] Systemic illness is usually mild, but 5–10% of CSD can develop various complications such as prolonged fever of unknown origin, pneumonia and/or pleural effusion, hepatosplenic manifestations, encephalopathy, osteomyelitis, and ocular disease.[5] Serological analysis for *B. henselae* is the mainstay of laboratory diagnostic tool of CSD. Sera with anti-*B. henselae* immunoglobulin G (IgG) titres of ≥1:256 or IgM titres of ≥1:20 are regarded as positive and indicate current or recent infection.[4,5]

The most common clinical presentation of melioidosis is pneumonia with or without septicaemia. Some *B. pseudomallei* infection can be latent and may present as chronic disease such as tuberculosis; hence, melioidosis is often referred to as the 'great mimicker'.[6] Apart from prolonged fever, localised lymphadenopathy, and subtle weight loss, our patient did not have other symptoms and signs to suggest systemic involvement of CSD or melioidosis. Undifferentiated fever, with no overt focus of infection, is another important manifestation, occurring in over 28% of children with melioidosis in Malaysia.[7] Patient's travel history during December school holidays, which is known as the raining season in certain parts of Malaysia, should raise the suspicion of melioidosis.

Confirmation of melioidosis is established by positive culture from blood, sputum, cerebrospinal fluid, or other specimens.8 Seroconversion or single high antibody titres (e.g. >160) by indirect haemagglutination assay (IHA) or enzyme-linked immunosorbent assay (ELISA) with consistent clinical features are also supportive for diagnosis of melioidosis.[8] In our case, there was a four-fold decrement of IgG and IgM titres after completion of antibiotics with clinical and radiological resolution, which supports the diagnosis. The additional finding of right subdiaphragmatic abscess in this case denotes the importance of ultrasonographic surveillance once there is evidence of melioidosis.

The typical course of CSD is usually benign and self-limiting in most cases.[4] Oral azithromycin is recommended for the treatment of mild to moderate disease for five days (10 mg/kg/dose on day 1, and 5 mg/kg/dose on days 2 to 5 as a single daily dose).[4] The use of azithromycin led to a more rapid resolution of lymphadenopathy.[9] The treatment for melioidosis consists of an intensive and eradication phase. During intensive phase, intravenous ceftazidime or carbapenem is given for 14 days followed by trimethoprim or amoxicillin-clavulanate for 20 weeks during the eradication phase.[10] It is fortunate that despite having fever and a subdiaphragmatic collection, our patient had a relatively mild disease as compared to adults, whereby the rate of severe sepsis and mortality is high due to presence of predisposing factors such as type-2 diabetes mellitus and chronic heart disease.

CONCLUSION

Our patient presented with undifferentiated prolonged febrile illness, significant travel history to a plantation situated in a melioidosis endemic area, and exposure to cats a week prior to developing symptoms. He had elevated immunoglobulin titres for both *B. henselae* and *B. pseudomallei* few weeks after admission. This case illustrates the importance of obtaining a detailed history and the need to have a high index of suspicion for cases with travel history to melioidosis endemic area and contact with cats. Imaging studies may suggest the diagnosis, and specific serology may confirm it, perhaps avoiding the need for biopsy.

ACKNOWLEDGEMENT

The authors thank the parents of the patient for their permission in writing this case report.

CONFLICT OF INTEREST

None to be declared by the authors.

CONSENT

Permission obtained from parent for this case report (see attached consent form).

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CASE REPORT

Colonic mucinous adenocarcinoma in a pregnant woman presented as pseudo Sister Mary Joseph's nodule: A case report

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SUMMARY

We report a case of a 41-year-old pregnant woman who initially presented with a sub-umbilical lump, for nearly five months. Subsequently, an ultrasound study was performed, and the patient underwent a surgical drainage operation for a presumed inflammatory condition, at the periumbilical region. The patient returned after a week post-drainage with a faecal discharging fistula. One month later, the patient had an emergency lower caesarean section plus bilateral tubal ligation because of the transverse lie of the foetus. One-month post-operative caesarean section, the fistula opening showed a big protruding ulcerating mass. En-bloc resection of the transverse and the descending colon was performed, and the histopathologic diagnosis showed a moderately differentiated mucinous adenocarcinoma. This case highlights that a high index of suspicion was recommended in an unresolved periumbilical lump (pseudo Sister Mary Joseph's nodule), and periumbilical metastasis of colorectal cancer frequently indicates advanced disease and poor prognosis. In view of its rarity of occurrence and limited experience, in the management of an ambiguous case, we report this case.

INTRODUCTION

Umbilical metastasis (Sister Mary Joseph's nodule) is an important physical finding. Cutaneous metastasis may occur through a direct extension of the tumour or lymphatic spread, intravascular dissemination, and surgical implantation.[1] Furthermore, there can be spread along the embryonal remnants such as the urachus in addition to the aforementioned mechanisms. We report a case of a 41-year-old pregnant woman who initially presented with a sub-umbilical lump, for nearly five months and was only later diagnosed to have metastatic disease. This case reveals the need for that a high index of suspicion when faced with an unresolving periumbilical lump (pseudo Sister Mary Joseph's nodule). Periumbilical metastasis of colorectal cancer frequently indicates advanced disease and poor prognosis. In view of its rarity of occurrence and limited experience in the management of an ambiguous case, we report this case.

CASE REPORT

A 41-year-old female, Gravida 6, Para 5, at 6 months of pregnancy, presented with a sub-umbilical enterocutaneous faecal fistula. Patient revealed that she complained of swelling near the umbilical region for nearly five months with recurrent vague abdominal pain, with an altered bowel habit, losing about 11 kg of body weight.

She also mentioned that late in March 2016, based on the report of an ultrasound study done at that time, she had underwent a surgical drainage operation for a presumed inflammatory condition near the umbilicus region. The patient returned after a week post-operatively with a sub-umbilical faecal discharging fistula. Then, patient was transferred to the general surgical department, Hospital Selayang.

Physical examination revealed that the patient was 7 months pregnant, with a viable baby and with sub-umbilical enterocutaneous faecal fistula; otherwise, the physical examination was unremarkable.
Full general laboratory tests were done.Apart from mild anaemia, all other results were unremarkable.

The enterocutaneous faecal fistula (ECF) was managed by using a colostomy bag for one month to give chance for the pregnancy to proceed further and to save the viable foetus. A month after the LCS, the ECF opening showed a large protruding ulcerating mass (Figure 1).

On the 18th of May 2016, the patient had an emergency lower caesarean section (LCS), with a bilateral tubal ligation due to the transverse position of the foetus.

On the 25th of June 2016, a computed tomography scan (CT scan) of the abdomen and pelvis was performed, which confirmed the presence of a large mass in the upper-central abdomen measuring approximately 15.5 × 10.5 × 11.5 cm (height × TR × AP).

The mass protruded through the anterior abdominal wall at approximately the level of the umbilicus, Infiltrating and extending through the anterior abdominal musculature and

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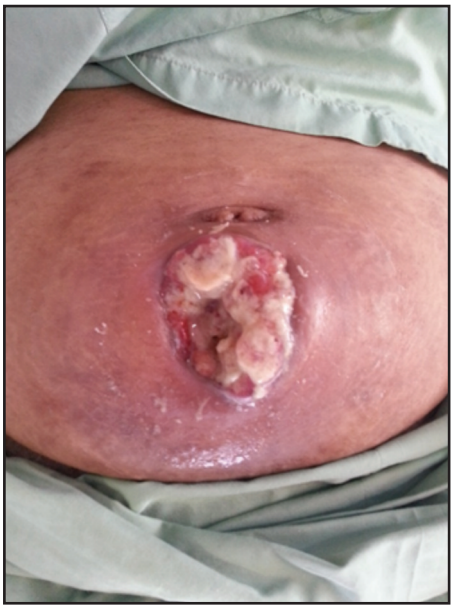

Fig. 1: Sub-umbilical enterocutaneous faecal fistula opening with a large protruding ulcerating mass.

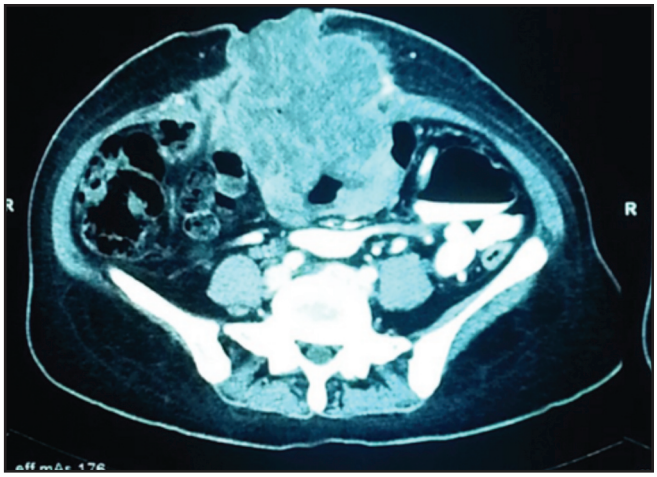

Fig. 2: Computed Tomography scan of the sub-umbilical region showed a large mass in the upper-central abdomen. The mass protruded through the anterior abdominal wall at approximately the level of the umbilicus.

extending to the skin as an ulcerated mass. There were lucencies of air within the mass, which may well have an irregular lumen (Figure 2).

The diagnoses were discussed with the patient and her family, and the patient consent was obtained for the proposed extensive surgical operation.

On the 25th of July 2016, the definitive surgery was done through a transverse elliptical incision, including the umbilicus with the fungating mass, cutting through the rectus sheath and muscles around the large infra-umbilical ECF and the tumour, which was found to be connected to the mid-transverse colon, also descending colon adhered and involved with the tumour mass, rectus muscles, and sheaths. En-bloc resection of the transverse and the descending colon was done, colonoscopy for the distal part of colon on table was done, no synchronous lesion was found, and left and right ureters were identified and preserved. A side-to-side anastomosis was performed with a GIA-100 stapler, between the ascending colon and sigmoid colon.

The left tensor fascia lata muscle was harvested and transplanted as an autologous graft. This procedure was performed to repair the defect in the remaining rectus abdominis sheath.

Histopathologic examination of the surgical specimen proved it as mucinous adenocarcinoma, moderately differentiated, and the tumour had directly invaded the abdominal wall.

DISCUSSION

In this case, the direct extension is the most probable way of spread, and the pregnancy with enlargement of the gravid uterus has the main impact to let the direct spread take place. Metastatic carcinoma can assume a variety of morphologic appearances. It usually presents as violaceous to a flesh-coloured, firm, freely mobile, painless nodules, single or multiple. It can sometimes mimic epidermal cysts, neurofibromas, lipomas, cicatricial morphea-like plaques, lymphoma, and alopecia. More rarely, it can mimic infection and present as a zone of pink to deep red or purplish-red indurated erythema with a well-demarcated border, a condition termed inflammatory metastatic carcinoma or carcinoma erysipelatoides.[2,3]

The presence of a skin lesion in the majority of cases indicates cutaneous metastases. However, further investigations are essential in order to rule out the possibility of a metachronous tumour, which can occur from 4 up to 30 years following an original resection. Therefore, the first line investigation should be the biopsy of a skin lesion followed by the full body CT to assess for the metastases elsewhere.[4,5]

CONCLUSION

Umbilical metastasis (Sister Mary Joseph's nodule) is an essential diagnosis to be identified. This case clearly highlights a rare but important physical finding as it is a sign of advanced stage of malignancy. A misdiagnosis in the initial stage of presentation of bacterial skin infection had been made without any evidence based on tissue cultures or biopsy. Therefore, any unexplained swelling, mass, or persistent cellulitis that does not respond to a short course of antibiotics therapy, should be seen by an experienced specialist and to be further investigated. The patient who had refused the initial suggestion for biopsy or surgical management, should have been counselled regarding the sinister possibilities of a non-healing lesion.

A few extremely vital key lessons to take from this case are as follows:

1. In cases like this, the patient must be directly referred to a specialist capable of performing proper radiological diagnostic procedures, as an early (accurate) diagnosis would have prevented these major complications.
2. Skin metastasis is an uncommon but significant occurrence that should not be overlooked since it often implies advanced pathology and a poor prognosis. Subsequent assessment should be carried out when any changes in the skin are noticed.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest to declare.

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A case series of pulmonary alveolar proteinosis: Response differently to whole lung lavage

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SUMMARY

Pulmonary alveolar proteinosis (PAP) is a rare disease and its prognosis can be improved by whole lung lavage (WLL). Herein, we present three cases with idiopathic PAP treated successfully with either single or double WLL in the same setting. All three of them presented with exertional dyspnoea with radiographic findings of pulmonary infiltrates. They showed a marked clinical and physiologic improvement post WLL. Two of them were in remission. These three cases were diagnosed using different lung biopsy modalities, including video-assisted thoracoscopic lung biopsy, computed tomography-guided percutaneous transthoracic tru-cut needle lung biopsy, and transbronchial forceps lung biopsy (TBLB), respectively. The current cases have shown that TBLB may provide adequate diagnostic yield, and the invasive surgical lung biopsy may not be necessary to achieve a definitive diagnosis.

INTRODUCTION

PAP is caused by defective alveolar macrophages that lead to alveolar accumulation of surfactants. PAP may result from mutations in granulocyte macrophage-colony stimulating factor receptor (GS-CSF) genes, autoimmune, toxic inhalation, or haematological disorders. We report case series PAP that responded to WLL at different degrees.

CASE REPORT

Case 1

A 41-year-old female presented in February 2011 with a 3-month history of cough and progressive shortness of breath on exertion. She was treated as a bronchial asthma but did not respond to the combination of inhaled budesonide and formoterol. She had a history of recurrent pneumonia and required bilevel positive airway pressure (BiPAP) six months before the clinic review.

Physical examination, routine blood tests, and antinuclear antibodies (ANA) were normal. Oxygen saturation was 95% in room air. A chest radiograph showed bilateral pulmonary reticulation. Spirometry showed a moderate restrictive ventilatory defect with forced expiratory volume in 1 s (FEV1) equal to 1.59 L (70.4% predicted), and forced vital capacity (FVC), 1.67 L (63.4% predicted). Static lung volume measurements revealed a total lung capacity (TLC) of 1.42 L (38.8% predicted) and residual volume of 0.16 L (14% predicted). Diffusing capacity for carbon monoxide (DLCO) was reduced at 1.06 L (18% predicted).

Contrasted chest computed tomography (CT) showed bilateral pulmonary infiltrates and thickened interlobular septa, a 'crazy paving' pattern (Figure 1A). Bronchoscopy revealed normal airways, and bronchoalveolar lavage (BAL) showed plaques of granular amphophilic in a background containing numerous bronchial lining cells, alveolar macrophages, and occasional squamous cells. Subsequent video-assisted thoracoscopic surgery (VATS) biopsy confirmed PAP.

The patient required WLL with saline solution in March 2012 (left lung 11.5L; right lung 13L), December 2012 (left lung 9L), March 2014 (left lung 13L; right lung 11L), and July 2019 (left lung 6L; right lung 6L). She had a marked ventilatory and radiological improvement after each WLL. To date, she remains asymptomatic with a stable lung function test.

Case 2

A 46-year-old female was first presented in 2010 with chronic cough and progressive dyspnoea on exertion for 12 months. She was being treated for bronchial asthma, but her symptoms were not a response to inhaled budesonide. She had two episodes of pneumonia, and she was dependent on home oxygen after the second episode of pneumonia.

Contrasted chest CT showed bilateral pulmonary infiltrates and thickened interlobular septa (Figure 1B). Bronchoalveolar lavage (BAL) revealed a milky white fluid. Microbiological analyses of BAL were negative. CT guide lung biopsy confirmed PAP. Her spirometry showed restrictive ventilatory defect with FEV1 equal to 1.35 L (48% predicted), FVC 1.37 L (42% predicted), and a normal FEV_1/FVC ratio of 98%. Her TLC was 1.94 L (46.5% predicted) and DLCO 0.88 L (16% predicted). The 6 min walking distance was reduced to 294 m.

She has required eight WLL since the diagnosis of PAP, and the last WLL was in 2018. A follow-up chest radiograph and high-resolution computed tomography showed evident regression of the ground glass opacities and interlobular septal thickening. To date, she remains asymptomatic with a stable lung function test.

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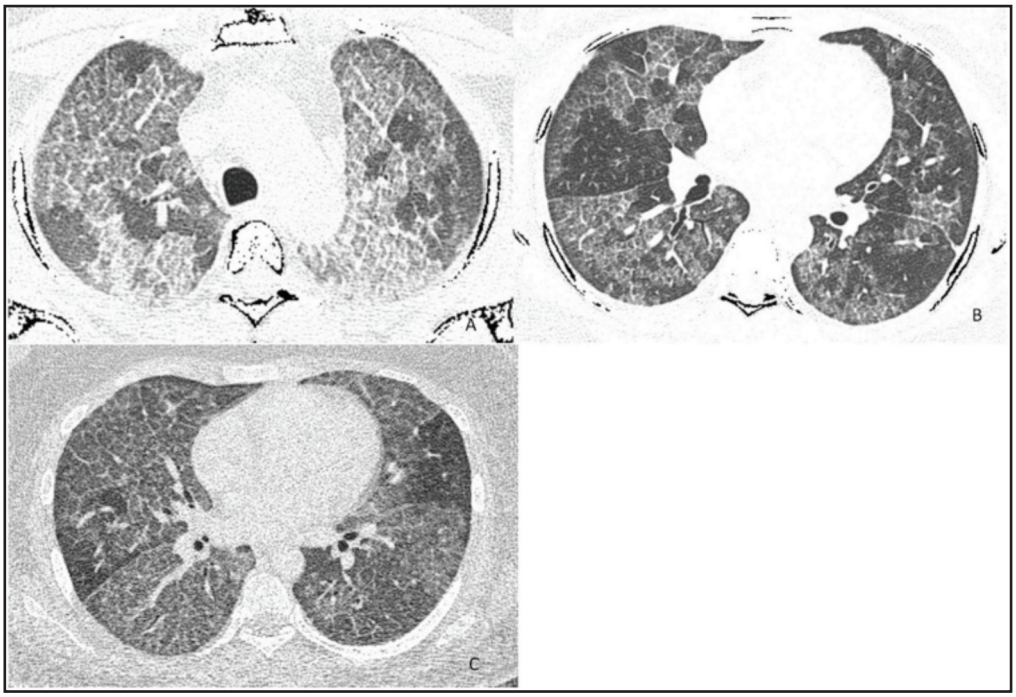

Fig. 1: Axial view CT thorax in lung window demonstrating cases of pulmonary alveolar proteinosis. (A) Case 1, (B) Case 2, (C) Case 3 with all scans showing patchy, "geographic" pattern of ground glass opacification superimposed on interlobular septal thickening in multiple lobes.

Fig. 2: Bronchoalveolar lavage specimens. (A) Normal BAL effluent. (B) Effluent obtained by WLL in pulmonary alveolar proteinosis, showing sedimentation of the proteinaceous materials at the bottom of the bottle.

Case 3

An 18-year-old girl was presented in September 2021 with intermittent cough and dyspnoea for two months with one week of fever. She was empirically treated as pulmonary miliary tuberculosis based on clinical symptoms and chest radiograph of diffuse miliary nodules. Her dyspnoea was not improved after two weeks, and she was subjected to chest CT followed by bronchoscopy with transbronchial forceps lung biopsy (TBLB). The CT showed a bilateral crazy paving pattern (Figure 1C).

BAL showed milky effluent. The BAL for mycobacterium tuberculosis cartridge-based nucleic acid amplification test and cultures were negative. Serum ANA was positive titres of 1:160, and extracted nuclear antibody was negative. Pulmonary function test showed restrictive ventilatory defects with the ratio of 98%, FEV1 of 1.89 L (65% predicted), FVC of 1.93 L (60% predicted), and reduced DLCO of 32%.

She underwent bilateral WLL in the same settings. Following the induction of general anaesthesia, she was intubated with a double-lumen endobronchial tube. Warm (36–37°C) sterile saline (0.9% saline) was instilled from the 1 L reservoir bag for each cycle. The WLL began with the left lung and repeats until the effluent is completely clear (Figure 2 A&B). She required ten cycles of lavage on the left lung and eight cycles on the right lung. After WLL, her oxygen saturation improved from 92% to 98% in room air. Repeated spirometry at one week showed improvements in FVC of 2.23 L (70% predicted) and DLCO of 36%.

DISCUSSION

PAP is classified into three categories: congenital, autoimmune or idiopathic, and secondary. The congenital forms are caused by mutations in the genes encoding surfactant protein B or C or the receptor for GM-CSF. Autoimmune PAP is associated with the presence of anti-GM-

CSF. Secondary PAP can be associated with infection, hematologic malignancies, or exposure to inhaled chemicals. Autoimmune PAP represents 90% of all PAP cases, and it is rarely associated with another autoimmune disease.[1] In all three of our patients, PAP is most likely to be the autoimmune PAP as there is no history of exposure to chemicals, and BAL excluded infection. They responded to the WLL at varying degrees. Two of the patients had achieved remission and did not require further WLL.

The diagnosis of PAP can be made with confidence based on typical HRCT thorax features in conjunction with milky BAL fluid. Transbronchial lung biopsy, VATS, or image-guided biopsy specimens provide a pathological feature that strengthens the diagnosis. Chest radiography generally reveals non-specific symmetric bilateral alveolar opacities. The major CT abnormalities are patchy, 'geographic' patterns of ground glass opacification superimposed on interlobular septal thickening in multiple lobes. The level of radiographic severity and clinical symptoms are often discrepant.[2] BAL typically has a milky appearance and may reveal foamy macrophages containing eosinophilic granules, with extracellular globular hyaline material and positive on periodic acid-Schiff (PAS) staining. Lung biopsy pathognomonically demonstrates intra-alveolar filled eosinophils, lipoproteinaceous materials with periodic acid–Schiff-positive and preserved alveolar architecture.
A pulmonary function test assesses disease severity and monitors the treatment response. The predominant abnormality is a restrictive ventilatory defect with a reduction in TLC and DLCO.

GM-CSF regulates surfactant homeostasis, macrophages maturation, and phagocytosis. Disrupted GM-CSF signalling by neutralizing GM-CSF autoantibodies is the aetiology of autoimmune PAP. This has led to ineffective alveolar macrophages clearance of the accumulated surfactant. The detection of anti-GM-CSF antibodies in peripheral blood and BAL using ELISA (enzyme-linked immunosorbent essay) can be used to diagnose autoimmune PAP. No association has been observed between anti-GM-CSF antibody levels and severity of autoimmune PAP, in terms of the decline in lung functions, decline in partial pressure of oxygen, or clinical symptoms.[1]

WLL is the first-line treatment of choice for PAP. WLL improves exercise tolerance, symptoms, pulmonary functions, arterial oxygenation, and macrophages function.[3] Radiological improvement occurs more gradually after the WLL and the time period varying between individuals.[4] WLL is indicated in a patient with limitation in daily activities because of dyspnoea, desaturation on the 6-min walking test, or PaO2 of less than 70 mmHg or a P(A–a) O2 of more than 40 mmHg as they are more likely to progress.[5]

WLL is a procedure for removing lipoproteinaceous material from pulmonary alveoli, thus improving macrophage function, arterial oxygenation, and shunt fraction. WLL is performed under general anaesthesia. The patient is intubated with a double-lumen endotracheal tube, with the non-lavage lung mechanically ventilated. Aliquots (1 L) of warmed (36–37°C) sterile saline is infused at a rate of approximately 100 mL/min into the lung and is allowed to drain to gravity. Manual or mechanical chest percussion is performed during the WLL. The process is repeated until the effluent is clear. The total volumes of saline required can range from 15 L to 40 L. Upon completing the procedure, bronchoscopic suction is performed to remove the residual isotonic sodium chloride solution. The controlateral lung may be lavage 24–48 h later.

PAP that responded to WLL generally carries a good prognosis. The patient may exhibit a different progression pattern, either a spontaneous improvement, stable disease, or worsened disease that requires frequent WLL.[1] The course of the disease varies, and severe pulmonary fibrosis is rare. Approximately 10% of patients experience complete spontaneous remission.[5] Granulocyte-macrophage colony-stimulating factor (GM-CSF), plasmapheresis, and rituximab can be considered an alternative therapy for refractory PAP.[6,7] Corticosteroids should not be used for PAP because of their potential to exacerbate opportunistic infections.

CONCLUSION

BAL, GM-CSF autoantibody levels plus tissues HPE is diagnostic in almost all cases. TBLB is a helpful adjunct as compared to invasive VATS or image-guided lung biopsy to obtain a histological diagnosis of PAP in conjunction with detailed clinical and radiological data. WLL is well tolerated and should be considered the first treatment modality in an experienced centre. Although PAP is a rare condition, recognizing the radio-pathological features and prompt diagnosis with WLL may improve the outcome.

CONFLICT OF INTEREST

The authors state that there is none to declare.

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CASE REPORT

Invasive *salmonella* enteritidis infection complicated by colonic perforations and pancytopenia: A case report

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SUMMARY

Salmonellosis caused by bacterial genus *Salmonella* is associated with a high morbidity and mortality rate. *Salmonellae* can be divided into typhoidal serotypes (S. enterica ser. Typhi and S. enterica ser. Paratyphi A) and nontyphoidal *Salmonella* (NTS) serotypes. The two most common NTS serotypes isolated from human sources were S. enterica ser. Typhimurium and S. enterica ser. Enteritidis. NTS infection can present with diverse clinical manifestations, including gastroenteritis, bacteraemia, septic arthritis, osteomyelitis, and endovascular infection. Intestinal perforation is an extremely rare and potentially fatal complication of severe salmonella infection. Herein, we report a case of invasive S. Enteritidis infection complicated by colonic perforation and pancytopenia. Following a colonic resection, the patient received a prolonged course of antimicrobial therapy and eventually recovered.

INTRODUCTION

Salmonella is one of the most commonly isolated foodborne pathogens, with over 2500 Salmonella serotypes identified to date. Infections caused by invasive serotypes of *Salmonella* are frequently fatal, necessitating appropriate and effective antibiotic therapy. Nontyphoidal *Salmonella* (NTS) infection can cause a wide range of clinical presentations, including gastroenteritis, bacteraemia, septic arthritis, osteomyelitis, and endovascular infection.[1] S. Enteritidis is the second most encountered serovar causing invasive NTS infections after serovar Typhimurium, accounting for approximately one-third of all cases. Contaminated hen's eggs were the most important vehicle of the S. Enteritidis infection.[2] Intestinal perforation is one of the most serious complications of *Salmonella* infection, and it can occur in patients who are not immunocompromised. Surgery is usually indicated in most cases of typhoid intestinal perforation, along with antibiotics and supportive care.[3]

CASE REPORT

An 18-year-old girl with no prior medical illness presented to Selayang Hospital, Malaysia with a three-week history of fever, diarrhoea, and abdominal pain. It was associated with malaise, reduced appetite, and weight loss. She denied having a headache, neck stiffness, blurred vision, or fitting episode. Two other members of the household also experienced similar but milder symptoms after consuming food bought from the market.

She was pale and delirious when she arrived at the hospital. She had a high-grade fever of 38.7°C and was normotensive but tachycardic. Her lungs were clear on auscultation, but her abdomen was distended and tender, with guarding. A neurological examination of the upper and lower limbs did not reveal any focal neurological deficit. The initial full blood count showed pancytopenia with a haemoglobin of 6 g/dL, white blood cell counts of 3×10^3/µL, and platelet counts of 90×103/µL. Blood gas analysis revealed metabolic acidosis with raised serum lactate of 3.3 mmol/L. The screening tests for HIV and connective tissue disease came back negative. An abdominal radiograph revealed grossly dilated large and small bowels, and a chest radiograph revealed no air under the diaphragm. The abdominal computed tomography (CT) scan revealed gross pneumoperitoneum suggestive of bowel perforation with tension pneumoperitoneum, but the brain CT scan revealed no abnormalities (Fig. 1).

The patient was intubated for respiratory failure on the same day of hospital admission, and empirical antibiotics were administered, including 2 g of intravenous ceftriaxone once daily and 500 mg of metronidazole thrice daily. She then underwent an emergency exploratory laparotomy, which revealed multiple punctate perforations in the splenic flexures of the colon, descending colon, and upper sigmoid colon. A segmental colonic resection was performed, and a double barrel stoma was created. After surgery, she was admitted to the intensive care unit and started on total parenteral nutrition. Meropenem was substituted for ceftriaxone due to persistent fever and to cover for nosocomial infection.

Salmonella spp was isolated from the blood culture and was later identified as S. Enteritidis by serotyping. The isolate was found to be susceptible to ampicillin and ceftriaxone. Histopathological examination of the affected colonic tissue revealed the presence of inflammatory infiltrates composed of neutrophils, lymphocytes, plasma cells, and histiocytes but no granuloma. There was no evidence of tuberculosis, cytomegalovirus, fungal infection, or malignancy. Her illness was complicated by intraabdominal collections and catheter related bacteraemia caused by extended-spectrum β-lactamases (ESBL)-producing Klebsiella pneumoniae, for which she received intravenous meropenem. A tracheostomy was performed as a result of the prolonged ventilation, and she was extubated after three weeks. Intravenous meropenem was administered for two weeks, followed by a prolonged course of ampicillin-sulbactam for six weeks. The pancytopenia resolved after antimicrobial therapy, so a bone

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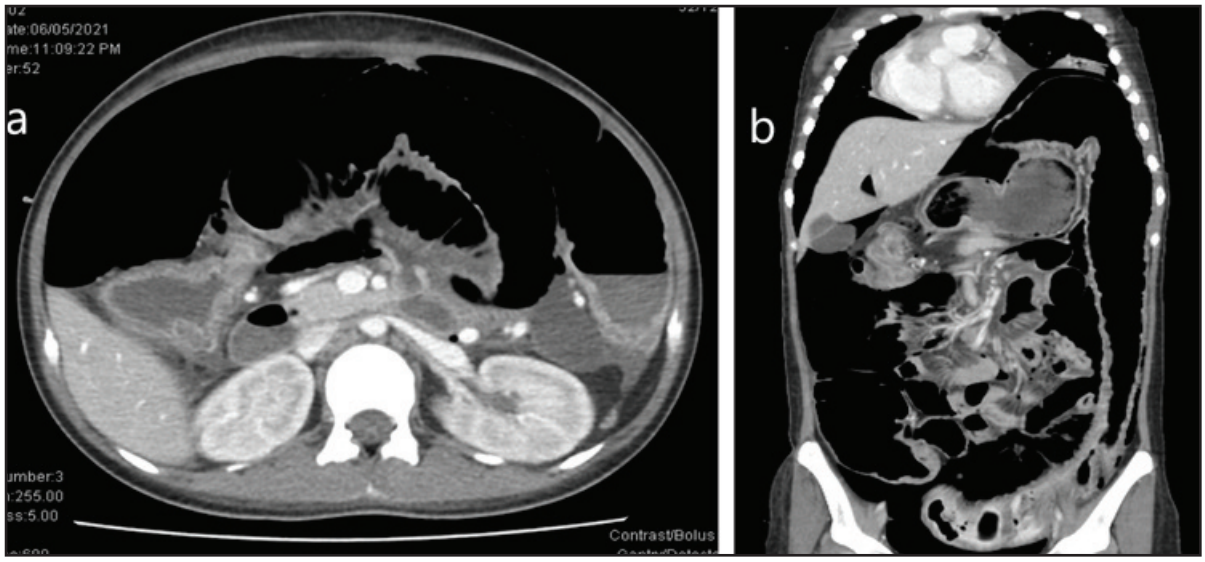

Fig. 1: Contrast-enhanced CT scan. (a) axial view and (b) coronal view of the abdomen revealing gross pneumoperitoneum suggestive of bowel perforation with tension pneumoperitoneum.

marrow examination was not required. A repeat CT scan of the abdomen revealed that the abdominal collections had resolved. She was discharged home and scheduled for stoma reversal at a later date.

DISCUSSION

Salmonella infection is still a major public health concern, especially in developing countries. Each year, it results in 93.8 million foodborne illnesses and 155,000 deaths. There are over 2600 different serovars of *Salmonella enterica*, which are divided into typhoidal and non-typhoidal *Salmonella*.[1,2] S. Typhimurium and Enteritidis are the major serovars implicated in invasive non-typhoidal Salmonella disease in Africa, accounting for more than 90% of cases.[4]

Salmonella gastroenteritis is characterised by nausea, vomiting, abdominal pain, and diarrhoea, which usually appear 48 hours after ingestion of food contaminated with the bacteria. In immunocompetent patients, it usually manifests as a mild, self-limiting disease, and requires no antimicrobial therapy other than hydration. It can, however, be life-threatening, presenting with bacteraemia and fever, and if left untreated, it can result in death. Invasive disease is more likely to develop in patients who have HIV, malaria, malnutrition, sickle cell anaemia, or are elderly.[3] Patients with invasive disease often have a fever and bacteraemia, and the clinical features can be non-specific, with different target organ involvement and complications such as pneumonia, endocarditis, mesenteric thickening and lymphadenopathy, hepatosplenomegaly, abscess formation, osteomyelitis, infective vascular aneurysm, pyelonephritis, and central nervous system manifestation such as meningitis.[5]

Although gastrointestinal tract infection is common with *Salmonella*, colonic perforation is rare and is one of the more serious complications.[5-7] Typhoidal disease has been linked to the majority of cases of colonic perforation. However, there have been several cases of colonic perforation associated with non-typhoidal *Salmonella* infection reported around the world.[6,7] For example, Hélias et al.[6] reported a case of spontaneous intestinal perforation due to S. Enteritidis in an otherwise healthy patient with no predisposing risk factors, which was very similar to our case. A study in the Netherlands confirmed that the use of H2 antagonists and proton pump inhibitors, as well as the consumption of raw eggs and products containing raw eggs, were linked to endemic S. Enteritidis infection.[8] We hypothesised that the patient had consumed food containing raw eggs contaminated with S. Enteritidis that had been purchased at a market. Otherwise, our patient had no other risk factors, such as HIV infection, malnutrition, or use of H2 antagonists or proton pump inhibitors.

The pathogenesis of colonic perforation caused by *Salmonella* infection is poorly understood. In the case of *Salmonella* typhi-related colonic perforation, it was demonstrated that bacteria infiltrating Peyer's patches caused necrosis, which led to haemorrhage and perforation. Another postulation is that an exaggerated immune system causes an increase in inflammatory cytokine production, which causes clumping of macrophages and lymphocytes around vascular tissue, leading to bowel necrosis.[9] On admission, our patient was diagnosed with pancytopenia, which was most likely caused by *Salmonella* infection. A case of severe pancytopenia in a patient with typhoid fever was previously reported, in which bone marrow examination revealed extensive haemophagocytosis, which contributed to pancytopenia.[10] In our case, her pancytopenia improved after antibiotic treatment, so a bone marrow examination was not required.

Treatment should include a laparotomy to identify the perforation site and resection of the necrotic segment as soon as possible. Antimicrobials with broad spectrum coverage and anaerobic coverage should be started. In patients with severe sepsis, such as our patient, adequate hydration and resuscitation are critical for maintaining hemodynamic stability.

CONCLUSION

Although the incidence of *Salmonella* infection has decreased significantly in developed countries due to the availability of effective antibiotics, it remains endemic in developing countries. Severe complications from nontyphoid S. Enteritidis, such as colonic perforation, are extremely rare and have a high morbidity and mortality rate. Early surgical intervention, effective resuscitation in the pre-operative period, post-operative care, and the use of appropriate antibiotics are all required for the optimal management of intestinal perforation.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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A case report of transverse myelitis in a patient with human immunodeficiency virus

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SUMMARY

Acute or subacute transverse myelitis is a rare disease caused by inflammation of the spinal cord. The extensive differential diagnosis of this disease require physician to timely decide the necessary investigations and plan for effective treatment. We report a case of anomalous multifactorial transverse myelitis in a patient with human immunodeficiency virus (HIV) who responded well with multimodal therapy. The patient was given immunosuppressive agent and plasma exchange for the demyelinating disease as well as antibiotics for neurosyphilis, antiviral for cytomegalovirus (CMV) neurologic disease, and highly active antiretroviral therapy (HAART). Three months after his first presentation, patient showed full neurology recovery and suppressed HIV viral load.

INTRODUCTION

Acute or subacute transverse myelitis is a rare disease that can cause devastating permanent disabilities in a young adult. The aetiology of transverse myelitis can be grouped into demyelination, autoimmune, infection, and paraneoplastic.[1] It is crucial for physicians to decisively investigate and timely initiate the right treatment. Those decisions will have an impact on the outcome of the patient. The clinical presentation of the disease depends on the extent of the spinal cord involvement with varying degrees of motor, sensory, and autonomic dysfunction. Primarily, after excluding compressive myelopathy by Magnetic Resonance Imaging (MRI), the evidence of spinal cord inflammation must be certain through the lumbar puncture findings of cerebrospinal fluid leucocytosis with raised protein. In HIV-infected patients, the management becomes more complicated as more potential opportunistic infections that affect the neurology need to be considered.

CASE REPORT

A 29-year-old male presented to Emergency Department after one week history of progressive lower limb weakness that affected the right leg, which then slowly progressed to the left leg within three days. He progressed from mild difficulty to walking and frequently tripping over the left leg to unable to stand steadily for one day. On the next day, patient developed acute urinary retention, resulting in a prompt visit to the Emergency Department. He has no fever, respiratory infection symptoms, or diarrhoea prior to the onset of weakness. He had no fall or trauma recently. There was no significant previous medical or surgical history.

Upon admission, his Glasgow Coma Scale (GCS) was 15. He was afebrile, blood pressure was 122/82 mmHg, pulse rate 87 was beats per minute, and respiratory rate was 18 breaths per minute with Spo2 98% on room air. Neurological examination revealed hypertonia of the right leg and normotonic left leg, reduced power over the right leg (grade 3/5) and left leg (grade 0/5). Hyper reflexes of bilateral knee, ankle jerk, and positive Babinski over the right side were reported. There was reduced sensation from T4 level downwards and loss of anal sphincter tone. There was no ulcer, rash, lymphadenopathy, joint tenderness, or swelling. Overall eye examination was normal with no signs of optic neuritis or uveitis. The other physical finding was unremarkable.

Routine laboratory investigations showed the following: haemoglobin level 12.3 g/dL, platelet count 269 x 109/L, white cell count 8 x 10^9/L, urea 4.1 mmol/L, sodium 137 mmol/L, potassium 3.8 mmol/L, creatinine 73 µmol/L, calcium 2.15 mmol/L, and albumin 43 g/L. He was biochemically euthyroid. HIV rapid test and subsequent HIV antibody test were positive. ESR was 27 mm/hour and C-reactive protein was less than 4 mg/L upon admission.

The initial chest radiograph and computed tomography (CT) scan of the brain were normal. The MRI of the spine was performed on the third day of admission and noted intramedullary enhancement of patchy high T2 signal with contrast enhancement at T4 to T6 level measuring 4.8 cm in length and another long segment intramedullary T2 hyperintense signal without significant contrast enhancement at T3 to T10 level likely to be syrinx. There was no evidence of spinal cord compression (Figure 1(A) and 1(B)).

Lumbar puncture was performed on the fourth day of admission. The opening pressure was 10 cmH2O. Cerebrospinal fluid (CSF) investigations revealed low glucose (1.78 mmol/L), high protein (1.17 g/L), and mild lymphocytosis. CSF India Ink test was negative, and gram stain was negative. Blood for CMV PCR was detected at log 1.34 but CSF test for CMV was not sent during the first lumbar puncture, and patient was not keen for repeat test. Syphilis

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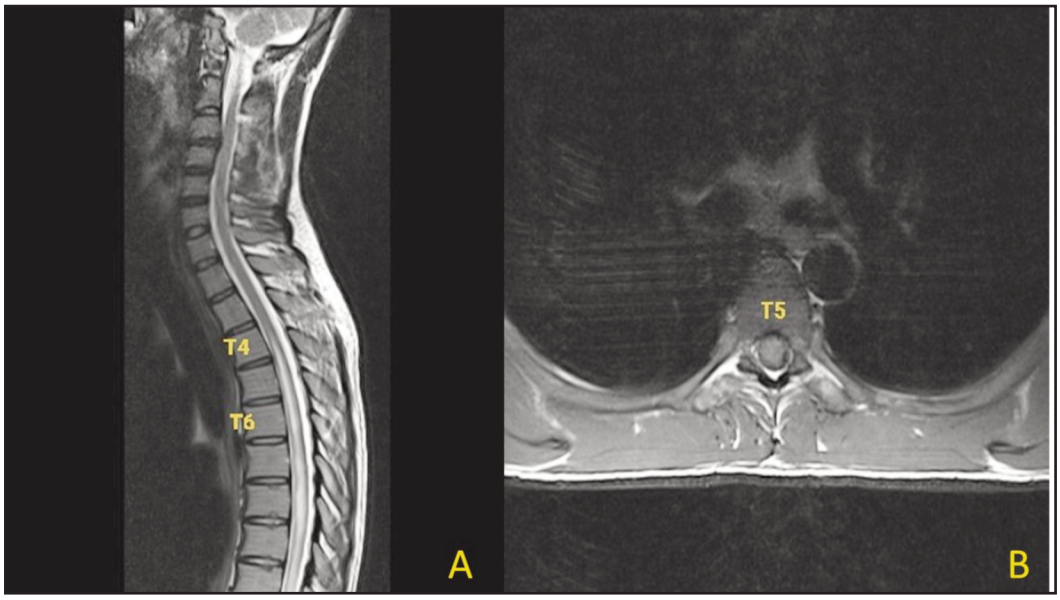

Fig. 1: T2-weighted Magnetic Resonance Image. (A) Sagittal view shows intramedullary enhancement of patchy T2 hyperintense lesion with contrast enhancement at T4 to T6 level (B) Axial view shows central intramedullary contrast-enhanced lesion at T5 level.

Types of treatment	Treatment received (day of admission)								
Antibiotic	IV Ceftriaxone then Benzylpenicillin (days 1–14)								
Corticosteroid		IV Methylprednisolone (days 4–8)	Followed by oral prednisolone (tapering dose)						stop
Plasma exchange				Plasma exchange (days 14, 16, 18)					
Antiviral				IV Ganciclovir (days 10–30)			Highly active antiretroviral therapy initiation (day 31)		*continue*
	Admitted						Discharged		
Neurological symptoms	Symptoms started	Symptoms worsened		Symptoms started to improve				Symptoms fully recovered	No new Symptom
Timeline of symptoms (week)	0	1	2	3	4	5	6	12	52

Fig. 2: Timeline of neurological symptom progression and treatment received by patient.

test was positive with VDRL titre of 1:32 but negative TPPA. Unfortunately, the most diagnostic neurosyphilis test such as CSF test for VDRL or FTA-ABS are not available in Malaysia.

He was initially treated with intravenous ceftriaxone on admission as empirical treatment for neurological infection and subsequently switched to benzylpenicillin as the first line therapy for neurosyphilis. Considering the possibility of demyelinating disease, on the fourth day of admission, patient was given a course of intravenous methylprednisolone, 1 g daily for five days, and followed by tapering dose of oral prednisolone. At day 10 of admission, intravenous ganciclovir was initiated to treat cytomegalovirus infection as the blood test genome was detected and as the clinical condition did not improve.

Plasma exchange was initiated at day 14 of admission after consultation from a neurology team in view of the poor response to the glucocorticoid therapy, concurrent antibiotic and antiviral treatment. Remarkable neurology

improvement was seen as the patient was able to stand with support after the third session of plasma exchange. His power over the right leg improved to grade 4/5 and left leg power improved to grade 2/5. However, plasma exchange was stopped after three sessions due to intravenous access issue.

In summary, he received a five-day course of intravenous methylprednisolone followed by tapering dose of oral prednisolone, three sessions of plasmapheresis on every other day, 14 days of treatment for neurosyphilis, and 21 days of treatment for CMV myelitis. Highly active anti-retroviral therapy (HAART) was initiated as soon as the patient completed the CMV treatment. His neurology deficit improved gradually and managed to be discharged after five weeks of hospitalisation with wheelchair and walking frame aided ambulation (Figure 2).

Some of the important pending results were reviewed after patient was discharged. The CSF oligoclonal band was detected, and other CSF results such as viral culture and mycobacterium tuberculosis culture were negative. Anti-nuclear antibody and anti-N-methyl-d-aspartate receptor (NMDAR) were all negative. The final diagnosis was revised as acute transverse myelitis due to demyelinating disease, CMV myelitis, and neurosyphilis.

After three months from the onset of neurology deficit, the patient was able to walk without aid to the consultation room during clinic review. There were no new symptoms, no residual leg weakness, or problem with urination. He complied with the HAART treatment and tapering oral prednisolone as advised. He is still on regular outpatient follow-up. The patient remains completely well until the recent review one year after the onset of the weakness.

DISCUSSION

Acute transverse myelitis can be the initial presentation of demyelinating disease. The two important points from this case that urged the decision for multimodal therapy approach are being in the common age group for the onset of demyelinating disease and the newly diagnosed HIV status.[1-3]

Multiple sclerosis is the most common demyelinating disease of the central nervous system and predominantly follows the clinical subtype of relapsing–remitting at disease onset. However, for this case report, there is still insufficient criteria to fulfil the requirements of diagnose multiple sclerosis diagnosis. Further MRI of the brain and spine follow-up as well as other tests at the neurology center such as evoked potential study, will be a valuable tool to consolidate the diagnosis.[3]

The degree of symptom resolution and recovery for demyelinating disease is variable. Plasma exchange can be beneficial in patients who do not respond to glucocorticoid therapy and may result in faster improvement of neurological symptoms as encountered in this case report.[1,4]
As for newly diagnosed HIV-positive patients who exhibited neurological symptoms, this may represent the first opportunistic infection in the central nervous system as the degree of immunosuppression was still uncertain. Although toxoplasmosis and tuberculosis are more common infections, in this case, there was no clinical evidence and investigation result to suggest such disease. Therefore, infective myelitis due to syphilis and CMV were considered.[5-7]

Generally, syphilitic myelitis is rare but it is the most potential curable form of neurosyphilis. It was previously reported that MRI spine finding of syphilitic myelitis showed high signal intensity in the T2-weighted images.5 Both syphilis and CMV myelitis may have abnormal cerebrospinal fluid analysis similar to the demyelinating disease, which are pleocytosis and raised protein.[5-7]

However, CMV infection commonly affects immunocompromised patient and may progress to end organ disease. Although neurological disease of CMV is rare, it may cause permanent disabilities without appropriate treatment. The association between the myelitis and the virus is still not well recognised but it may represent a postinfectious transverse myelitis.[1,6,7] In this instance, the patient is often treated with antiviral drugs and corticosteroids.

The most conclusive investigation to diagnose CMV infection in cerebrospinal fluid is by CMV polymerase chain reaction (PCR).[7] Unfortunately, the CSF sample was not sent for the test in this case. However, treatment was started as soon as the CMV detection by serum PCR in order to not miss out the golden time to treat the disease. Subsequently, HAART was initiated just after the completion of intravenous ganciclovir. After the acute phase, rehabilitative care is the next important step to improve functional skills and to prevent secondary complications from immobility. It is crucial to begin occupational and physical therapies early during recovery. In this case, the patient started to show neurological improvement at the second week of hospitalisation. He continues to improve with treatments and rehabilitation programs and neurologically recovered after three months.

The prognosis of the transverse myelitis is variable as the primary disease can be the main contributing predictor. Generally, infectious myelitis will have a better outcome with prompt treatment. However, for demyelinating disease such as multiple sclerosis, the patient needs to be followed up longer to determine the clinical subtypes and to evaluate new evidence of neurology deficit periodically before concluding the long-term prognosis.[2,3]

CONCLUSION

Acute transverse myelitis has always been a challenging disease to be treated at a non-neurologist centre. The practical approach to manage acute transverse myelitis in a young HIV-infected patient would be ideal to follow the sequence from infection, demyelination, and autoimmune disease. However, the less common aetiology such as paraneoplastic myelitis should also be explored if the patient did not respond to the initial treatment given. This case was reported to promote awareness among physicians of the possible aetiologies for transverse myelitis in immunocompromised patient.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Early-onset neonatal hypocalcaemia secondary to maternal vitamin D deficiency in an infant with DiGeorge syndrome: A first case report in Malaysia

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SUMMARY

DiGeorge syndrome is a genetic disorder that is related to a wide range of defects affecting various parts of the body. The clinical expression shows marked variability making the diagnosis often missed or underdiagnosed. Here, we describe a neonate who presented with loud inspiratory stridor secondary to hypocalcaemia at birth. Physical examination revealed no abnormality other than evidence of congenital cardiac defect. Laboratory evaluations confirmed the diagnosis of maternal vitamin D deficiency that led to symptomatic hypocalcaemia in the newborn infant. The presence of hypocalcaemia coupled with episodes of recurrent infections led to the clinical suspicion of DiGeorge, which was later confirmed by fluorescence in situ hybridisation test.

INTRODUCTION

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome, affects approximately one in 4000–7000 children globally.[1] This disorder is characterised by embryological dysgenesis of the third to fourth pharyngeal pouches and fourth branchial arch, which is related to wide range of defects affecting various parts of the body.[1,2] Due to its' incomplete penetrance, there is a marked variability in clinical expression of DGS. The classical features of this syndrome often include conotruncal cardiac anomalies, palatal cleft with specific facial appearance, hypocalcaemia, and thymic hypoplasia with secondary impaired T cell response, which leads to immunodeficiency.[1,2] Affected individuals may also have other associated problems such as kidney abnormalities, hearing loss, autoimmune disorders including rheumatoid arthritis or Grave's disease, and delayed psychomotor development with a tendency to develop seizures, learning disability as well as psychiatric illnesses.[1,3,4]

Transient neonatal hypocalcaemia is a well-recognised feature of DGS. It is typically associated with aplasia or hypoplasia of the parathyroid glands. However, neonatal hypocalcaemia secondary to maternal vitamin D deficiency in an individual with DGS has never been reported. This is believed to be the first case of early-onset symptomatic neonatal hypocalcaemia secondary to maternal vitamin D deficiency in a neonate who was later diagnosed with DGS in Malaysia.[5,6]

CASE REPORT

A female infant was admitted to the neonatal intensive care unit (NICU) for severe respiratory distress at birth. She was born at 38 weeks of gestation via spontaneous vertex delivery with a birth weight of 3680 g. The mother was a 35-year-old with no pregnancy-related complications. The baby cried immediately after delivery; however, the baby was noted to have loud inspiratory stridor immediately. Her respiratory rate was 65 breaths per minute associated with deep intercostal and subcostal recession. Pulse oximeter oxygen saturation was 85% on bag valve mask ventilation of 100% oxygen; hence, she was intubated, stabilised, and transferred to NICU. A direct laryngoscopy visualised no structural abnormalities that could explain the stridor. Further clinical assessment revealed no obvious dysmorphism, pulse rate was 120 beats/minute, blood pressure was 80/45 mmHg, and body temperature was 36.6°C. A grade three systolic murmur was heard on chest examination; other systemic review was unremarkable.

Despite optimum ventilatory support, the infant remained cyanosed and oxygen saturation ranged between 85% and 90%. Arterial blood gases showed pH 7.36, pCO2 39.2 mmHg, pO_2 43 mmHg, and HC03 21.5 mmol/L. Chest radiograph revealed a boot-shaped heart and a prominent thymic shadow (Figure 1). A bedside echocardiogram confirmed the diagnosis of Tetralogy of Fallot with the presence of major aorto-pulmonary collateral arteries (MAPCAs). Further evaluation disclosed a persistently low corrected serum calcium level (1.37 mmol/L) associated with a low serum 25-hydroxy D level for both the baby and the mother (29.76 nmol/L and 10.21 nmol/L, respectively) and normal serum parathyroid hormone level (20.8 ng/L), which suggest a diagnosis of vitamin D deficiency. The serum magnesium level was also low (0.67 mmol/L), and serum alkaline phosphatase as well as phosphate levels were normal (228 U/L and 1.95 mmol/L, respectively). She responded well to calcium and vitamin D supplements, evident by the gradual increase in her serum calcium level and magnesium levels after one week (2.02 mmol/L and 0.71 mmol/L), at one month (2.0 mmol/L and 0.78 mmol/L) and at two months (2.15 mmol/L and 0.89 mmol/L), respectively. Due to recurrent lung infections, she remained on respiratory support until day 77 of life. Apart from recurrent lung infections, she developed two episodes of septicaemia with no bacteria isolated from her blood cultures. Her infections were

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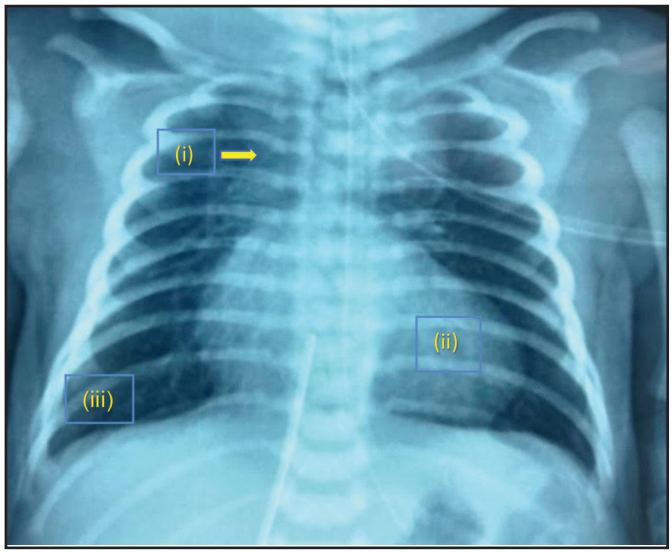

Fig. 1: Chest radiograph at birth revealing (i) a boot-shaped heart with (ii) prominent thymic shadow, and (iii)clear lung fields.

presumptively treated for Methicillin Resistant Staphylococcus Aureus (MRSA) as she had nasal colonisation of MRSA. The constellation of cardiac anomalies, hypocalcaemia, and recurrent infections has led to the clinical suspicion of DGS, which was later corroborated by the presence of heterozygous deletion at chromosome 22q11.2 on fluorescence in situ hybridisation (FISH) test. Her immune functional status was evaluated, and the results were within normal parameters for her age.

DISCUSSION

Inspiratory stridor, which is found in this case, requires immediate evaluation to determine the underlying aetiology. A complete diagnostic workup is crucial especially in the presence of significant airway obstruction causing respiratory distress as seen in our case. Interestingly, the most important preliminary finding in our patient was hypocalcaemia. Inspiratory stridor presenting immediately after delivery is not only a rare presentation of neonatal hypocalcaemia but also potentially harmful. Acute laryngospasm caused by reflex closure of the larynx, resulted from hypocalcaemia in our case. Severe laryngospasm has the risk of causing significant hypoxia with resultant developmental delay, particularly in areas of neurocognitive development. Studies have shown that neonates with hypocalcaemia have a higher predictive index of developing intellectual disability.[4]

It is fair to conclude that hypocalcaemia in our case was due to insufficient levels of vitamin D. Although infrequently contributes to early-onset hypocalcaemia, maternal vitamin D deficiency is a well-recognised cause of neonatal hypovitaminosis D and neonatal hypocalcaemia.[7] Vitamin D deficiency during pregnancy results in poor transplacental transfer of vitamin D and calcium and thus reduced stores in the newborn.[8] Majority of these infants present with symptomatic hypocalcaemia with seizures, jitteriness, or less commonly stridor by the second week of life. Parathyroid hormone (PTH) levels are usually elevated in the presence of hypocalcaemia; however, it was not seen in this case. The unexpected normal PTH levels may be due to the immature calcium-vitamin D-PTH axis, as well due to the presence of concomitant hypomagnesemia. Hypomagnesemia inhibits PTH action and concurrently reduces sensitivity at target organs. The possibility of neonatal hypoparathyroidism in this case could not be ruled out.

Hypocalcaemia secondary to hypoparathyroidism in individuals with DGS was first described by DiGeorge.[9] Hypoparathyroidism in this population is often mild manifesting as a phenomenon of decreased parathyroid reserve. The affected individual may be normo-calcaemic most of the time but predisposed to hypocalcaemia during periods of stress or illness, during which they may not be able to mount elevated PTH level and therefore unable to fully correct hypocalcaemia. The key point here is to regularly monitor the serum calcium as well as the PTH level. Hypovitaminosis D in patients with DGS in not unexpected. The state of hypoparathyroidism impairs the conversion of renal 25-hydroxyvitamin D (25[OH]D) to active form 1,25-dihyroxyvitamin D.8 Unlike as seen in our case, vitamin D deficiency caused by hypoparathyroidism manifests later in life. The long-term effect of vitamin D deficiency caused by hypoparathyroidism can increase the risk of mental health disorders such as schizophrenia and depression.[10]

Our patient showed a good response to vitamin D and calcium supplements and was able to maintain normal serum calcium levels after discontinuation of supplements. Homeostasis of circulating calcium levels in individuals with DGS can be easily disrupted due to multiple reasons. The formation of thymus and parathyroid glands from the third and fourth pharyngeal pouch indicates a strong relation between the two. Although the presence of thymic shadow coupled with normal PTH levels may indicate the presence of the parathyroid gland, the function may be still impaired due to low reserves.[1] This inadvertently predisposes individuals with DGS to recurrent transient hypocalcaemia due to failure in maintaining calcium homeostasis. Ideally, vitamin D levels, serum PTH levels, and magnesium levels should be re-

evaluated again at a three-to-four-month interval until the age of one year and then annually to objectively ascertain the treatment outcome of this neonate.[4]

CONCLUSION

Hypocalcaemia is an unusual but potentially life-threatening cause of inspiratory stridor at birth. This case highlights the importance of an immediate and complete evaluation of the underlying aetiology. Neonatal vitamin D deficiency secondary to maternal hypovitaminosis D is prevalent and is the main aetiologic factor for symptomatic neonatal hypocalcaemia. The presence of associated cardiac defect and recurrent episodes of infection have also led to the diagnosis of DGS.

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CASE REPORT

Pulmonary arteriovenous malformations: A case of missed diagnosis in a neonate

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SUMMARY

Pulmonary arteriovenous malformation (PAVM) is a congenital vascular abnormality that can cause persistent cyanosis in children. PAVMs can go undetected till adulthood; however, there have been several neonatal cases reported over the years. This case report describes a classical manifestation of a child with isolated PAVM whose diagnosis was likely missed during the neonatal period. A high level of clinical awareness of this condition is crucial as early diagnosis and appropriate treatment can prevent life-threatening complications and mortality. Diagnosis was confirmed by computed tomography pulmonary angiography and percutaneous transcatheter embolotherapy resulted in complete resolution of symptoms.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are structurally abnormal vessels that provide communication between the branches of pulmonary arteries and pulmonary veins.[1] PAVM creates an intrapulmonary right-to-left shunt and allows the systemic venous blood to bypass the normal pulmonary capillary bed, which is crucial for gas exchange and filtration process.[1] Majority of cases presenting with PAVM eventually manifest with hereditary haemorrhagic telangiectasia; however, in a small group of patients, it appears to be sporadic.[2] PAVM is most commonly congenital in origin, but the condition often remains silent until adulthood, suggesting that the gradual enlargement of the PAVM occurs with increasing age.[3] Although PAVM is a rare clinical problem in neonate, it can be potentially fatal. Therefore, a thorough assessment is essential for early diagnosis.[4]

CASE REPORT

A three-year-old girl presented with a one-month history of worsening cyanosis and deteriorating effort tolerance. She was born prematurely at 33 weeks of gestation at a district hospital and reported to have respiratory distress at birth requiring continuous positive airway pressure (CPAP) support. Chest radiographs revealed a homogenous opacity over the right upper and middle lobes (Figure 1), and she was treated for congenital pneumonia with intravenous antibiotics. She responded well and successfully weaned off respiratory support by day 8 of life. As clinical improvement pursued, no repeat chest radiograph was done. She was referred to our centre for further evaluation of systolic murmur at 1 month of age, and echocardiography showed a patent ductus arteriosus with left pulmonary artery stenosis. However, no chest radiography was performed. She subsequently defaulted follow-up, and parents claimed that she was well with no history of fever, cough, recurrent respiratory infections, or cyanosis. There was also no history of epistaxis, haemoptysis, or skin telangiectasia. Parents denied any family history of cardiac condition or hereditary haemorrhagic telangiectasia.

Physical examination revealed that the child was cyanosed with digital clubbing and was in respiratory distress. Transcutaneous oxygen saturation was 69% before dropping to 55% when she raised from supine to upright position despite being put on supplemental oxygen 3 L/min via nasal prong. Her mucous membrane was normal. Cardiovascular examination was unremarkable; however, auscultation of the lungs revealed a bruit over the right middle zone that was more prominent at sitting position. She had polycythaemia with haemoglobin level of 15.7 g/dL. The chest radiograph showed a homogenous opacity over the right upper and middle lobes of the lungs (Figure 2). A bedside echocardiogram demonstrated a structurally normal heart with no evidence of pulmonary hypertension. However, the transthoracic contrast echocardiography (TTCE) was highly suggestive of PAVM. The diagnosis was confirmed by computed tomography pulmonary angiography (CTPA), which showed a multiple complex PAVM, predominantly in the anterior segment of the right upper, middle, and lower lobes.

The PAVMs were successfully embolised via a percutaneous transcatheter. Post-embolotherapy, no significant residual flow was seen through the PAVMs. Percutaneous pulse oximetry saturation on room air increased immediately from 70% to 100%. Her postoperative course was uneventful, and she was discharged after four days. Her exercise tolerance improved, and she remained asymptomatic with good weight gain during the three-month follow-up.

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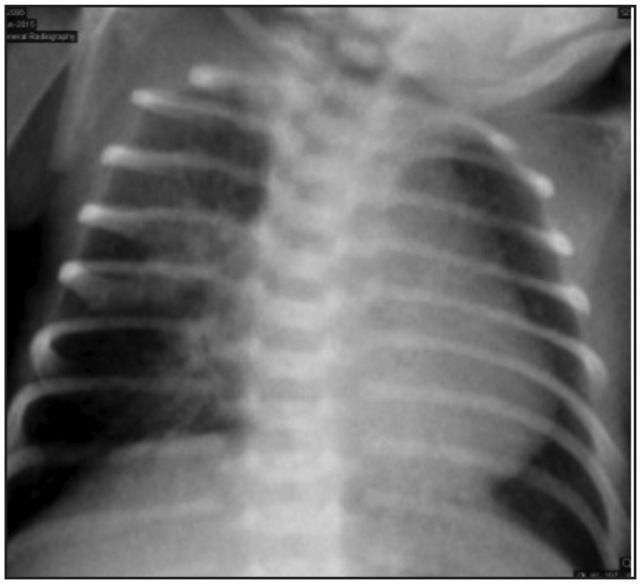

Fig. 1: Chest radiograph at birth showed a homogenous opacity over right upper and middle lobes.

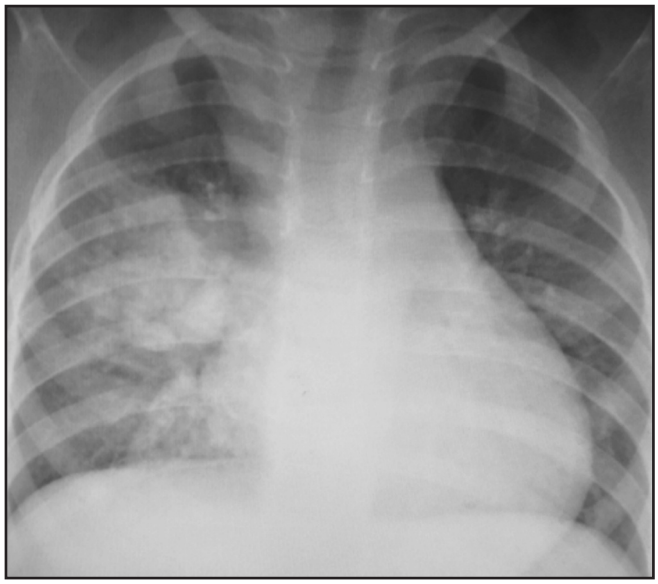

Fig. 2: Chest radiograph taken at three years of age showing similar opacities.

DISCUSSION

Over the past decades, PAVM has evolved from a rare curiosity to not an uncommon anomaly with an estimated prevalence of 1 in 2600 individuals.[5] Numerous reviews and reports have documented the classical presentation and natural history of PAVM in adults and children; however, manifestation in the neonatal period is rare.[4] Although majority of PAVM is congenital in origin, in most cases, it remains silent until adulthood with only 10% of cases detected among children.[6]

Our patient presented with the classic triad of dyspnoea, cyanosis, and clubbing accompanied by pulmonary bruit and orthodeoxia, the hallmark of PAVM. The latter is the result of worsening ventilation/perfusion mismatch due to gravitationally induced redistribution of blood flow to the lung bases where the vascular malformations are located when the patient is in an upright position.[5] Our suspicion was supported by the classical appearance of a sharp, well-defined nodule or mass of uniform density on the chest radiograph as well as the appearance of microbubbles seen in the left side of the heart through transthoracic contrast echocardiography following the injection of agitated saline. The latter technique has high sensitivity (100%) but lower specificity (67%–91%).[3] PAVM in our case was diagnosed via the gold standard imaging study that clearly delineates the exact anatomy of the anomaly. With CTPA, PAVM can be accurately predicted in 95% of cases, thus making it a necessary investigation for therapeutic planning.[3]

Interestingly, a retrospective review of our patient's chest radiograph suggests that she may have had the abnormality since neonatal period; however, the diagnosis was missed as she showed significant clinical improvement with supportive therapy and no documented cyanosis. Thus, no repeat imaging study performed to look for resolution of the radiological evidence. Furthermore, PAVM is not routinely appreciated during standard echocardiogram and may be deceptive.[4] Missed diagnosis of PAVM in the neonatal period is not uncommon.[4,6] The chest radiograph findings were often misinterpreted as pneumonia or pulmonary hypertension. Fortunately, our patient did not exhibit a more devastating or life-threatening manifestation such as stroke, cerebral abscess, haemoptysis, or haemothorax.[4,7] These are related to either loss of filtration function of the lung, leading to paradoxical systemic embolisation, or rupture of the abnormal vascular structure.

Our patient was successfully treated with percutaneous transcatheter embolotherapy. The main aim of the treatment is early occlusion of the fistula to alleviate hypoxia and to prevent any serious thromboembolic complications owing to paradoxical embolisation. Although it is highly effective and safe, embolotherapy may be potentially complicated by haemorrhage, arrhythmias, air embolism, or migration of the embolic agent.[7] In 5%–15% of cases, recanalisation after re-embolisation is warranted. Surgical intervention is reserved for cases with serious bleeding, lesions not amendable to embolotherapy, or failure of embolotherapy.[7]

CONCLUSION

Although PAVMs are rarely manifested in the neonatal period, the unspecific chest radiographs findings should raise suspicion. A high level of awareness is crucial as early diagnosis and appropriate treatment can prevent life-threatening complications and avert death.

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