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

Chapter in Book
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World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

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Knowledge and attitude towards children's oral health: findings from a sample of first-time mothers in Malaysia

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ABSTRACT

Introduction: Women's important roles within families which include modelling appropriate oral health behaviours require them to have good knowledge and positive attitude in oral health. This study determined knowledge and attitude towards children's oral health among first-time mothers and factors associated with the attributes.

Materials and Methods: A total of 154 first-time mothers in the third trimester of pregnancy who attended two health clinics in the state of Sarawak, Malaysia for antenatal care participated in this cross-sectional study. A structured self-administered questionnaire was used to measure the variables of interest.

Results: Most mothers could correctly identify the aetiological factors of dental caries and strategies for preventing the disease in children. However, a substantial portion could not identify certain cariogenic and non-cariogenic foods or drinks. Most pregnant women have appropriate attitudes towards children's oral health although some showed unfavourable attitude about care of primary teeth. Women who were older and had attended a talk on children's oral health were more likely to have higher mean knowledge score than their respective counterparts, and higher mean knowledge score was associated with higher mean attitude score.

Conclusion: Most first-time mothers in this study had correct knowledge and favourable attitude about children's oral health, although misunderstandings and misperceptions in several issues were also common. Significant association found between experience of attending oral health talk and oral health knowledge, and between oral health knowledge and attitude, substantiate the importance of an educational intervention program to optimise the mothers' roles in caries prevention in children.

KEYWORDS:
Oral health; knowledge; attitude; pregnant women

INTRODUCTION

Early childhood caries (ECC) is defined as 'the presence of one or more decayed (non-cavitated or cavitated lesions), missing (due to caries), or filled surfaces, in any primary tooth of a child under age six year'.[1] ECC is one of the most prevalent diseases in children, with a pooled global prevalence of 48%.[2] Affecting more than 530 million children globally,[3] ECC is largely untreated.[4] In Malaysia, the latest survey in 2015 revealed a high caries prevalence among 5-year-old children at 71.3%.[5]

ECC is a major public health issue not only because of its high prevalence and impact on the health and wellbeing of the child and the family members, but also cost to society.[6,7] With concerted efforts, ECC can be controlled and prevented.[7] In addition to a collaborative approach involving the dental and other stakeholders to bring about development of policies and programmes to reduce the burden of ECC, educating parents regarding the causes and prevention of ECC by delivering customised recommendations and specific parenting practices remains an important strategy.[7]

Parents play an important role in establishing their children's oral health behaviour from a young age.[8] In early childhood, a learned behaviour, including oral health behaviour, is established by the repetition of any form of work that provides opportunities for the child to develop a skill or knowledge area. Ozbek et al.[9] have reported that oral health behaviour of the parents is copied by their children. Adequate knowledge towards children's oral health has been shown as an important risk factor associated with parents' good oral health practices and subsequent favourable oral health status of the children.[8,10] In addition, positive oral health attitude of the parents can also provide learning, support, and a family norm of good oral health practice.[11] Hence, it is essential that parents have correct oral health knowledge and positive oral health attitude so that they can successfully undertake the responsibility of being the correct role-models for their children.

Pregnancy has been described as a time when women often have increased motivation and are particularly receptive to improve their lifestyle and health behaviours.[12] For the first-time mothers, perceptions about risks to the health of the child seem to be the primary driving force for these changes.[12] Community trials and systematic review of randomised controlled trials suggest that oral health education intervention to pregnant women may reduce the risk and prevalence of ECC in their children.[13,14] Oral health program for antenatal mothers in Malaysia has been in place since the early 1970s.[15] Targeting pregnant women who attend the Ministry of Health maternal and child health clinics for their

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prenatal check-up, this program aims to create awareness among expectant mothers on the importance of oral health, empowering them to become the agent of change who can stimulate behavioural changes in their families.[15]

However, after more than 50 years, the program did not seem to achieve a satisfactory outcome; the uptake of primary oral health care services among antenatal mothers was relatively low at 44.4% in 2022 compared to the percentage of mothers receiving prenatal care at the Ministry of Health maternal and child health clinics that has been consistently above 95% since 2010,[16] and the prevalence of caries among 5-year-old children in 2015 was also high despite the decline from 76.2% in 2005.[5] One of the probable reasons this program has yet to achieve its intended objective is because the increased motivation for healthy lifestyle and behaviour changes was assumed without considering the women's risk perceptions as well as the capability and opportunity to engage in these changes.[12] Understanding the baseline knowledge and attitude towards children's oral health, which is the perception of risk, is seen as an important foundational step in planning an improved pregnancy-specific intervention program. In this study, we investigated the knowledge and attitude of first-time mothers towards children's oral health care and factors associated with their knowledge and attitude.

MATERIALS AND METHODS

Study Design and Study Population

This was a cross-sectional study among pregnant women who received antenatal care from two government clinics in Malaysia between October 2021 and February 2022. This study was conducted in Sarawak, the largest state in Malaysia in the northwest of Borneo Island. Sarawak is divided into 12 divisions, and this study was conducted at Tudan Health Clinic in Miri Division and Bintulu Health Clinic in Bintulu division. The selection of these health facilities was based on the similarities in socio-demographic characteristics of the served population, health and oral health care services provided. Both Tudan Health Clinic and Bintulu Health Clinic are in the town area of the respective division. Both facilities provide similar primary health care services including antenatal health care services and oral health care services. The maternal and child health care clinic and the dental clinic are located within the same building of the respective health clinic.

First-time mothers in the third trimester of pregnancy, aged 18 years and above, without any diagnosed cognitive disorders, and able to read and write in Malay language, were eligible to participate. The sample sizes for all specific objectives of this study were calculated, and the largest affordable sample size was yielded from the objective to determine children's oral health knowledge of the pregnant women using the formula to estimate a single proportion with a 95% confidence interval (CI). The proportion was estimated at 63% which was the proportion of pregnant women who knew that primary teeth start to erupt at the age of 6 months.[17] At a precision of 0.08, the largest affordable sample size of 140 was yielded. In anticipation of 10% non-response rate, a sample size of 154 was determined for this study. The ethical approval to conduct this study was obtained from the Universiti Sains Malaysia Human Research and Ethics Committee (USM/JEPeM/21050377) and the Ministry of Health Malaysia Medical Research and Ethics Committee [NMRR-20-2141-55603 (IIR)].

Research Tools

A self-administered questionnaire developed by Noor Zamry et al.[18] was used to assess knowledge and attitude towards children's oral health among the participants. The questionnaire was in Malay language with 30 items assessing the knowledge domain and 12 items assessing the attitude domain. The response options for all items were closed-ended; 'true', 'false' and 'don't know' options were given for the knowledge items and a 5-point Likert scale rating of 5 for 'strongly agree', 4 for 'agree', 3 for 'neither agree nor disagree', 2 for 'disagree', and 1 for 'strongly disagree' were given for the attitude items. Additionally, a structured form was used to collect information on demographic profile of the participants (age, highest education level, employment status and monthly household income), last dental visit, and experience of attending a talk on children's oral health.

Data Collection

Non-proportionate stratified random sampling was used to obtain equal numbers of samples from each maternal and child health care clinic, and systematic random sampling method was applied for selection of pregnant women who attended the clinics during the study period and fulfilled the study criteria. Following explanation about the study objectives and procedures, written informed consent was obtained from the women who agreed to participate. Participating pregnant women were informed that their participation in this study would be voluntary and they are free to withdraw from the study at any time. It was also emphasised that the questionnaire was anonymous, and confidentiality of data is ensured. Instructions on questionnaire completion were provided prior to the questionnaire administration. The questionnaire completion took place in a special room with good lighting and low level of noise. The time taken by most of the participants to complete the questionnaire was between 10 to 15 minutes. The questionnaire was collected immediately following completion.

Statistical Analysis

Data processing and analysis were done using the IBM SPSS software, version 26. Descriptive statistics were used to obtain the frequency and percentage (%) of categorical variables and the mean and standard deviation (SD) or median and interquartile range (IQR) of continuous variables. Linear regression analysis was performed to investigate the factors associated with children's oral health knowledge and attitude among participants. For this analysis, a mark was given to each response for all 30 knowledge items and 12 attitude items. For each knowledge item, one mark was given for correct responses, and zero mark was given for incorrect and don't know responses. For the attitude items, a mark of 1 to 5 were given according to the response given on the Likert scale, except for the negatively worded items that were re-coded in reverse direction so that a higher mark on each item indicated better attitude. The marks were later summed up to

obtain the overall score for each domain. The total knowledge score may range between 0 to 30, and the total attitude score between 12 to 60, with a higher score indicating a better knowledge and attitude respectively. In the regression analysis, starting with simple linear regression analysis, the following independent variables were tested: age, education level, employment status, monthly household income, last dental visit, and exposure to oral health talk. In addition, the mothers' mean knowledge score was tested as a potential factor associated with their attitude towards children's oral health (mean attitude score). In multiple linear regression analysis, variables were selected using forward selection, backward elimination, and stepwise selection methods. The selected variables were examined for any two-way interactions using the LR test and multicollinearity issues using the variance inflation factor (VIF) test. Assumptions of linearity, normality, and equal variance of the regression model were examined using residual plots. Presence of outliers were also identified, indicated by data points beyond +3.0 and -3.0 of standardised residuals. The final model is presented with adjusted regression coefficient and 95% (CI), t-statistics and P value. The level of significance for this analysis was set at P value of less than 0.05.

RESULTS

All the 154 participants completed the questionnaires, giving a response rate of 100%. Table I shows the characteristics of the study participants. The age of the participants ranged from 18 to 36 years with a mean of 26.7 years (SD = 5.09). Most participants received at least secondary education (88.3%), and more than half (60.4%) were unemployed with medium monthly household income on RM3,500 (IQR 2500), which is below the threshold of RM4,850 for the 40% of low-income earners in Malaysia.[19] Almost half (46.8%) had visited dentists within the past year, and slightly more than a quarter (27.3%) had attended a talk about children's oral health.

Knowledge Towards Children's Oral Health

Table II shows the knowledge towards children's oral health among the participants. Most participants knew that the first baby tooth will erupt at the age of 6–9 months (77.9%) and a baby's mouth should be cleaned even before the first tooth erupts (87.7%). Most pregnant women in this study also knew that dental plaque causes dental caries (74.7%), and that a child's teeth should be brushed at least twice daily (91.6%), particularly before bedtime (87.0%). Most participants also knew that a white spot on the tooth surface is an early sign of dental caries (78.6%), which can be prevented using fluoride toothpaste (72.7%) and were aware of the appropriate amount of fluoride toothpaste to be used in children.

More than half of participants (69.5%) knew that dental caries can affect children below 2 years of age, but only less than half of the women knew that children of mothers with caries are at risk of developing caries themselves (40.1%). Most women knew that frequent intake of sugary foods (93.5%) and pooling of milk in the mouth during sleep (74.7%) can cause dental caries. However, about half were unaware that fruit juice (54.5%), white bread (53.2%), baby biscuits (46.8%), bananas (59.7%), and dried fruits such as dates (51.9%) and raisins (47.4%) have a high potential to cause dental caries. In addition, some (40.3%) mistakenly thought that breast milk was highly cariogenic, and another 24.7% were unsure.

Attitude Towards Children's Oral Health

Table III shows the attitude of the participants towards their children's oral health. Most participants had positive attitude and agreed on the importance of baby teeth (strongly agree = 51.9%, agree = 42.9%), the need to brush the newly erupted teeth (strongly agree = 42.9%, agree = 32.5%) at least twice daily (strongly agree = 63.0%, agree = 33.8%), and the need for them to supervise the toothbrushing (strongly agree = 63.6%, agree = 33.1%). Most women also agreed that they need to encourage their child to drink from a cup by 1 year of age (strongly agree = 29.9%, agree = 38.3%), make sure their child does not take sweet and sticky foods (strongly agree = 53.2%, agree = 42.9%), and bring their child for dental check-up before 1 year of age (strongly agree = 54.5%, agree = 35.7%).

However, a considerable proportion of the participants also showed unfavourable attitude about care of primary teeth by agreeing that primary teeth need not be given good care as they will be replaced by permanent teeth (strongly agree = 15.6%, agree = 17.5%) and carious baby teeth need not be given attention (strongly agree = 12.3%, agree = 11.7%). More than half of the women also agreed (strongly agree = 30.5%, agree = 36.4%) that permanent teeth will not last a lifetime.

Factors Associated with Knowledge Towards Children's Oral Health

The mean knowledge score was 19.5 (SD = 5.66) with the lowest score of 2.0 and the highest score of 29.0. Table IV shows results of linear regression analysis of factors associated with knowledge on children's oral health among the participants. Multiple linear regression analysis showed a significant positive relationship between age of the participants and their mean knowledge score (p = 0.003). More specifically, older women had higher mean knowledge score than those who were younger. Another factor found to be significant with the knowledge score was experience of attending a talk on children's oral health. Women who attended the talk had higher mean knowledge score than those who did not (p = 0.013). With these two significant variables, the model explained 9.3% of the variance in the knowledge score (R^2 = 0.093). Possible two-way interactions between variables were not significant and no multicollinearity issue was detected. All model assumptions were met, and no outliers were found.

Factors Associated with Attitude Towards Children's Oral Health

The mean attitude score was 36.2 (SD = 4.85) with the lowest score of 22.0 and highest score of 48.0. Of the tested independent variables, knowledge score was the only variable found to be significantly associated with the attitude score at both simple and multiple variable analysis (Table V). Mothers with higher mean knowledge scores had higher attitude scores (p<0.001). A one-unit increase in knowledge score resulted in a 0.39-unit increase in attitude score (95% CI:0.26-0.51).

Table I: Characteristics of participants (n = 154)

Variable	Frequency (%)
Age (Year)*	26.7 (5.09)*
Education level	
No formal education	2 (1.3)
Primary education	16 (10.4)
Secondary education	83 (53.9)
Post-secondary (e.g., diploma, vocational)	35 (22.7)
Tertiary education	18 (11.7)
Employment status	
Yes	61 (39.6)
No	93 (60.4)
Monthly household income (MYR)	3500 (2500)**
Last dental visit	
Within 1 year	72 (46.8)
Within 1-2 years	26 (16.9)
More than 2 years ago	31 (20.1)
Never had dental examination	25 (16.2)
Ever attended oral health talk	
Yes	42 (27.3)
No	112 (72.7)

*Mean (SD)
**Median (IQR)

Table II: Knowledge towards children's oral health (n = 154)

Variable	Frequency (%)		
	Correct	Incorrect	Don't know
Calcium intake during pregnancy helps in the formation of strong teeth	134 (87.0)	2 (1.3)	18 (11.7)
The first baby tooth will erupt at the age of 6–9 months	120 (77.9)	2 (1.3)	32 (20.8)
Plaque is a white layer containing bacteria that accumulates on tooth surface	121 (78.6)	1 (0.6)	32 (20.8)
Plaque can cause dental caries	115 (74.7)	2 (1.3)	37 (24.0)
Frequent intake of sugary foods can cause dental caries	144 (93.5)	3 (1.9)	7 (4.5)
Children are at risk of dental caries if they fall asleep with milk pooling in the mouth	115 (74.7)	14 (9.1)	25 (16.2)
Tooth decay can affect children below 2 years of age	107 (69.5)	7 (4.5)	40 (26.0)
Early sign of caries can be seen as a white spot on the tooth surface	121 (78.6)	1 (0.6)	32 (20.8)
Children of mothers with caries are at risk of developing caries themselves	63 (40.1)	25 (16.2)	66 (42.9)
Foods or drinks with high potential to cause dental caries:			
Formula milk	86 (55.8)	24 (15.6)	44 (28.6)
Breast milk	54 (35.1)	62 (40.3)	38 (24.7)
Fruit juice	70 (45.5)	41 (26.6)	43 (27.9)
Fortified drink	99 (64.3)	24 (15.6)	31 (20.1)
White bread	72 (46.8)	43 (27.9)	39 (25.3)
Chocolate	128 (83.1)	11 (7.1)	15 (9.7)
Baby biscuit	82 (53.2)	37 (24.0)	35 (22.7)
Banana	62 (40.3)	58 (37.7)	34 (22.1)
Dates	74 (48.1)	41 (26.6)	39 (25.3)
Peanut	36 (23.4)	77 (50.0)	41 (26.6)
Sweets	131 (85.1)	11 (7.1)	12 (7.8)
Cheese	19 (12.3)	102 (66.2)	33 (21.4)
Raisin	81 (52.6)	38 (24.7)	35 (22.7)
Sticky dessert	108 (70.1)	18 (11.7)	28 (18.2)
A baby's mouth should be cleaned even though the teeth have not yet erupted	135 (87.7)	3 (1.9)	16 (10.4)
Dental plaque can be removed with toothbrushing	113 (73.4)	11 (7.1)	30 (19.5)
A child's teeth should be brushed twice daily	141 (91.6)	5 (3.2)	8 (5.2)
Brushing before bedtime is essential	134 (87.0)	6 (3.9)	14 (9.1)
Fluoride toothpaste can be used to prevent dental caries	112 (72.7)	8 (5.2)	34 (22.1)
Only a smear of fluoride toothpaste is needed to brush teeth of children below 3 years old	112 (72.7)	7 (4.5)	35 (22.7)
Only a pea size of fluoride toothpaste is needed to brush teeth of children above 3 years old	112 (72.7)	7 (4.5)	35 (22.7)

Table III: Attitude towards children's oral health (n = 154)

Variable	Frequency (%)				
	Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
Baby teeth are important	80 (51.9)	66 (42.9)	6 (3.9)	2 (1.3)	0 (0.0)
Carious baby teeth need not be given attention	19 (12.3)	18 (11.7)	12 (7.8)	85 (55.2)	20 (13.0)
Baby's teeth need not be given a good care as they will be replaced by permanent teeth	24 (15.6)	27 (17.5)	15 (9.7)	75 (48.7)	13 (8.4)
Premature loss of baby teeth due to caries can affect the normal eruption of the permanent teeth	64 (41.6)	62 (40.3)	22 (14.3)	4 (2.6)	2 (1.3)
Permanent teeth will not last a lifetime	47 (30.5)	56 (36.4)	25 (16.2)	20 (13.0)	6 (3.9)
A baby's mouth needs to be cleaned even though the teeth have not yet erupted	96 (62.3)	46 (29.9)	9 (5.8)	3 (1.9)	0 (0.0)
I need to brush my child's newly erupted teeth	66 (42.9)	50 (32.5)	27 (17.5)	11 (7.1)	0 (0.0)
I need to make sure my child brushes teeth twice daily	97 (63.0)	52 (33.8)	5 (3.2)	0 (0.0)	0 (0.0)
I need to supervise my child's toothbrushing	98 (63.6)	51 (33.1)	5 (3.2)	0 (0.0)	0 (0.0)
I need to encourage my child to drink from a cup by 1 year of age	46 (29.9)	59 (38.3)	40 (26.0)	8 (5.2)	1 (0.6)
I need to make sure my child does not take sweet and sticky foods	82 (53.2)	66 (42.9)	5 (3.2)	0 (0.0)	1 (0.6)
I need to bring my child for dental check-up before 1 year of age	84 (54.5)	55 (35.7)	14 (9.1)	1 (0.6)	0 (0.0)

Table IV: Factors associated with mean knowledge score (n = 154)

Variable	Simple linear regression		Multiple linear regression		
	Crude b (95% CI)	p value	Adjusted b (95% CI)	t-statistics	p value
Age (Year)	0.26 (0.09, 0.43)	0.004	0.26 (0.09, 0.43)	3.04	0.003
Education level					
No formal education/primary/secondary*					
Post-secondary/tertiary	0.18 (-1.73, 2.08)	0.854	-	-	-
Employment status					
No*					
Yes	0.82 (-1.02, 2.67)	0.380	-	-	-
Monthly household income (MYR)	0.0 (0.00, 0.00)	0.159	-	-	-
Last dental visit					
More than 1 year ago/Never*					
Within 1 year	2.01 (0.23, 3.79)	0.027	-	-	-
Ever attended oral health talk					
No*					
Yes	2.44 (0.45. 4.43)	0.017	2.48 (0.53, 4.42)	2.52	0.013

* Reference category

Table V: Factors associated with mean attitude score (n = 154)

Variable	Simple linear regression		Multiple linear regression		
	Crude b (95% CI)	p value	Adjusted b (95% CI)	t-statistics	p value
Age (Year)	0.06 (-0.10, 0.21)	0.209	-	-	-
Education level					
No formal education/primary/secondary*					
Post-secondary/Tertiary	0.53 (-1.10, 2.16)	0.522	-	-	-
Employment status					
No*					
Yes	0.46 (-1.12, 2.05)	0.563	-	-	-
Monthly household income (MYR)	-0.00 (0.00, 0.00)	0.910	-	-	-
Last dental visit					
More than 1 year ago/never*					
Within 1 year	0.46 (-1.09, 2.01)	0.558	-	-	-
Ever attended oral health talk					
No*					
Yes	1.32 (-0.41, 3.04)	0.135	-	-	-
Knowledge score	0.39 (0.26, 0.51)	<0.001	0.39 (0.26, 0.51)	6.20	<0.001

* Reference category

DISCUSSION

Pregnancy has been described as the time when women are more motivated to adopt healthy behaviour.[20] ECC intervention during pregnancy therefore becomes important as women may be particularly receptive to oral health education message with subsequent changes in behaviour to keep their child's mouth healthy.[13,14] Becoming a parent for the first time can be physically and emotionally intense as mothers navigate a major life transition without the benefit of experience.[21] First-time mothers need clear and comprehensive information and instructions on children's oral health care as part of their preparation for motherhood. Understanding the women's knowledge and attitude towards children's oral health can help the oral health care providers to be more focused in planning an antenatal education program to reduce the risk and prevalence of ECC.

Parents' knowledge about nutrition has been shown to be an important determinant of their food choices and nutritional intake.[22] Most of the mothers in this study knew about the role of calcium to help ensure formation of strong teeth, although calcium was commonly reported to be deficient in pregnant women.[23] Women in our study were also mostly aware about the etiological factors of dental caries including dental plaque and sugary foods, although a substantial proportion of participants did not know that formula milk, fruit juice, white bread, baby biscuits, bananas, dates, and raisins that are commonly given to children, also have high potential to cause dental caries. On the other hand, foods with low potential to promote dental caries like breast milk, peanut and cheese were incorrectly thought to be cariogenic. Most of our findings are in agreement with the results reported by Noor Zamry et al.[18] in a study among pregnant women in Kelantan, a state in the northeast of Peninsular Malaysia. Comparable findings from two studies conducted in different settings in Malaysia indicate the likelihood that the results can be generalised to the larger population. Recognising the important role of diet in caries development,[24] a re-look into the current oral health education message to antenatal mothers is therefore indicated as parents are highly motivated by health and nutrition, in addition to the child's taste preferences, when choosing foods for their children.[25] Mothers should be educated about strategies to translate their health motivations into healthy food choices and feeding practices for their family, including the ability to correctly identify cariogenic foods and drinks and take the appropriate preventive strategies.

Erroneous knowledge about the cariogenic potential of breast milk among the first-time mothers in this study should be of concern as it may deter the women's intention to breastfeed after delivery. Breast milk is the best source of nutrition for infants, and its bioactive components can provide protection against infection and inflammation.[26] The Government of Malaysia is committed to promote and support breastfeeding through development of the National Breastfeeding Policy, in line with the World Health Organization recommendations.[27] While breastfeeding should be encouraged among the first-time mothers, the women must also be cautioned against night-time breastfeeding. Although breast milk has low cariogenic potential, the pooling of milk around teeth during sleep can increase the risk for dental caries.[28] The medical professionals and breastfeeding advocates are in an excellent position to advise mothers that the benefits of breastfeeding should not be imperilled by the increased risk for caries due to improper feeding habit. It is good to note that most women in our study were aware that the pooling of milk in the mouth can contribute to the development of dental caries.

ECC is highly preventable,[29] hence oral health care should begin as soon as the first primary tooth erupts between 6 and 9 months of age which was correctly identified by most pregnant women in this study. Most first-time mothers in this study could correctly answer questions regarding caries prevention, particularly oral hygiene care and use of fluoride toothpaste. There is good evidence that higher dental caries rate is associated with lower toothbrushing frequency, and the effect is more pronounced in the deciduous than in the permanent dentition,[30] giving credence to the general toothbrushing recommendation of at least twice daily.[31] Most participants in this study were aware that a child's teeth should be brushed twice daily, and that brushing before bedtime is essential. Saliva flow is greatest during the waking hours of the day and diminishes considerably during sleep.[32] Hence, toothbrushing before bedtime is recommended not only to remove plaque and all traces of food, but also to allow fluoride to remain in the mouth for a prolonged time and not be quickly cleared by the saliva.[31]

Parental knowledge on children's oral health have a significant impact on the oral health status of their children.[33] Children whose mothers had good oral health knowledge were less likely to have ECC when compared with children whose mothers had poor oral health knowledge.[10] Furthermore, children of mothers with active caries are at risk of developing caries themselves,[34,35] and only less than half of mothers in this study knew about this risk. The relationship between oral health of young children and that of their mothers was attributed to poor oral health behaviour of the mothers.[34,35] This evidence concurs the important role of mothers in oral health care of their children by modelling and imparting correct oral health information, positive oral health attitude, and appropriate oral health care practice, and mothers should be made aware of their important roles.

Parental attitude to children's oral health has a direct significant influence on their preventive oral health behaviors.[11] While most first-time mothers in our study showed favourable attitude towards children's oral health, a considerable proportion also had unfavourable attitude with regards to care of primary teeth, including carious primary teeth. The consequences of having untreated carious teeth can extend beyond pain, infection, and eating difficulties.[36] Disturbed sleep, loss of school days, reduced activity, visits to emergency departments, and hospitalisations, can negatively affect the young children's health-related quality of life with significant social and economic consequences for the family, and cost to the society.[36] Primary teeth are important to maintain space for the permanent teeth developing underneath. Early loss of primary teeth due to caries will allow the adjacent teeth to move into the space and block the erupting permanent teeth, leading to crowding and future orthodontic issues.[37] Findings of this study suggest the need

for intervention programs to educate mothers about the importance of primary teeth and to teach essential skills needed to effectively perform preventive oral hygiene care for their children.

Factors previously shown to be associated with mothers' knowledge include age, education level, and household income.[38,39] In this study among first-time mothers, the influence of education level and household income on the mothers' knowledge was not apparent. However, the age of the mothers and experience of attending a talk on children's oral health were found to be significantly associated with their knowledge. Our study also found that women who had better knowledge about children's oral health were more likely to have favourable attitude. These findings substantiate the benefit of providing oral health education intervention to antenatal mothers geared to improve their knowledge and attitude, which have been shown to be important predictors of preventive oral health behavior.[8,40]

Our study adds to the growing body of evidence on knowledge and attitude of mothers towards children's oral health care and factors associated with their knowledge and attitude. While there have been a considerable number of studies reporting the knowledge and attitude of mothers towards children's oral health care, literature on first-time mothers is scarce. Nevertheless, this study has a limitation related to the integral issue of using a self-administered questionnaire due to the subjectivity of responses that depend on the participants' honesty and motivation to answer.

CONCLUSION

Most first-time mothers in this study have correct knowledge and favourable attitude towards children oral health. However, a substantial proportion were not aware of the positive association between mother and child caries experience and could not identify foods commonly given to children as cariogenic including formula milk, baby biscuits, and bananas. Instead, foods with low potential to promote dental caries like breast milk was incorrectly thought to be cariogenic. In addition, some had unfavourable attitude about care of primary teeth and believed that permanent teeth will not last for life. Age and experience of attending a talk on children's oral health were significantly associated with the mothers' knowledge, which in turn, was found to be associated with their attitude towards children oral health.

Our findings substantiate the benefit of providing oral health education intervention to first-time mothers that is geared towards optimising the roles of mothers as the agent-of-change in controlling and preventing ECC. A well-planned program using suitable and easy-to-understand oral health education materials is indicated to make sure the mothers are equipped with adequate information on children's oral health that may promote development of positive attitude and subsequent favourable preventive oral health behaviour.

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The potential role of artificial intelligence-assisted chest X-ray imaging in detecting early-stage lung cancer in the community—a proposed algorithm for lung cancer screening in Malaysia

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ABSTRACT

Introduction: The poor prognosis of lung cancer has been largely attributed to the fact that most patients present with advanced stage disease. Although low dose computed tomography (LDCT) is presently considered the optimal imaging modality for lung cancer screening, its use has been hampered by cost and accessibility. One possible approach to facilitate lung cancer screening is to implement a risk-stratification step with chest radiography, given its ease of access and affordability. Furthermore, implementation of artificial-intelligence (AI) in chest radiography is expected to improve the detection of indeterminate pulmonary nodules, which may represent early lung cancer.

Materials and Methods: This consensus statement was formulated by a panel of five experts of primary care and specialist doctors. A lung cancer screening algorithm was proposed for implementation locally.

Results: In an earlier pilot project collaboration, AI-assisted chest radiography had been incorporated into lung cancer screening in the community. Preliminary experience in the pilot project suggests that the system is easy to use, affordable and scalable. Drawing from experience with the pilot project, a standardised lung cancer screening algorithm using AI in Malaysia was proposed. Requirements for such a screening programme, expected outcomes and limitations of AI-assisted chest radiography were also discussed.

Conclusion: The combined strategy of AI-assisted chest radiography and complementary LDCT imaging has great potential in detecting early-stage lung cancer in a timely manner, and irrespective of risk status. The proposed screening algorithm provides a guide for clinicians in Malaysia to participate in screening efforts.

KEYWORDS:
Lung cancer; cancer screening; artificial intelligence; chest radiography; low-dose computed tomography

INTRODUCTION

Lung cancer is one of the most common forms of cancer worldwide, accounting for 11.4% of newly diagnosed cancer cases in 2020, with Asia accounting for approximately 60% of all new cases.[1,2] It is the leading cause of cancer-related mortality globally, resulting in approximately 1.8 million deaths, or 18% of cancer-related deaths in 2020.[1] In Malaysia, lung cancer accounts for approximately 10% of cancer cases and is a leading cause of cancer-related mortality.[3,4] Lung cancer records the lowest observed survival of all reported malignancies in the country (5-year survival rate of 9.0%; 95% confidence interval 8.4 to 9.7).[5]

The poor prognosis has been largely attributed to the fact that most patients present late with advanced stage disease.[6] Data from the National Cancer Institute of the United States of America indicate that comparatively high 5-year relative survival rates (61.2%) were observed for individuals presenting with localised disease.[7] MySCan similarly reported gradually reduced 1-year, 3-year and 5-year relative survival with increasing stages of lung cancer.[5] Hence there is an urgent unmet need for improved, accessible, cost-effective and less invasive approaches for identification, risk assessment and prioritisation of screening in high-risk individuals.[8] This has led to extensive research into molecular biomarkers[8,9] and diagnostic algorithms[10,11] to complement existing screening methods.

Low dose computed tomography (LDCT) has been widely touted as the optimal modality for lung cancer screening by several bodies, but its implementation in Malaysia has been sporadic and opportunistic at best.[6] LDCT screening in at-risk populations, namely those with a significant tobacco

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smoking history, has been truly life-saving with an impressive (20 to 61%) reduction in lung cancer-specific mortality, driven by impactful stage shift with the detection of more early-stage tumours.[12,13] Early-stage disease is more amenable to treatments with a curative intent. Surgical resection as part of multi-modal therapy in medically fit patients offers the best long-term prognosis in terms of disease-free survival and overall survival.[14,15] Early-stage lung cancer treatment is considerably cheaper.

Screening for lung cancer, however, is an imperfect science. A systematic review by the US Preventive Services Task Force suggests that screening high-risk individuals with LDCT may produce false-positive results, leading to unnecessary and invasive procedures, overdiagnosis, increased distress, and to a lesser extent, radiation-induced cancers.[16] In addition, lung cancer screening is also hampered by the cost of and accessibility to LDCT imaging. Alarmingly, in Asia including Malaysia, the incidence of lung cancer in non-smokers continues to rise, especially in women and those of Oriental ethnicity. Air pollution and family history have emerged as significant risk factors in never-smokers. The TALENT study, which confirmed the effectiveness of LDCT screening in a pre-defined, never-smoker high-risk population with an impressive early lung cancer detection rate of 2.6% (superior to the NELSON study), provides compelling evidence to screen for the disease in at-risk families due to the genetic predisposition evinced by the rising risk with the more first-degree relatives one has with lung cancer.[12,17] However, based on current LDCT screening guidelines, detection of lung cancer in the non-smoker or never smoker remains elusive. Therefore, there is a pressing need for an innovative yet practicable approach to facilitate early detection of lung cancer in non-smokers.

Chest radiography is proposed as an initial step to precede LDCT in lung cancer screening, given its ease of access and affordability. It allows screening in a wider population, which circumvents the issue of low-risk individuals not being screened. Chest radiography may also help reduce the rates of overdiagnosis with LDCT. Historically, chest radiography was used as a screening tool for lung cancer, but hampered by lower accuracy and diagnostic yield. The use of artificial-intelligence (AI)-assisted chest radiography, however, is superior to conventional historical imaging and is expected to improve the detection of an indeterminate pulmonary nodule (IPN), which may represent an early lung cancer. Patients with IPNs can then be appropriately counselled and further investigated with an LDCT. Published data suggests the incorporation of AI can enhance the diagnostic sensitivity of chest radiographs (from 66.4 to 74.7%) and reduce the number of false positive findings per radiograph from 0.25 to 0.18.[18] The technology is especially helpful for junior or trainee radiologists and general physicians. For the detection of lung cancers visible on the chest radiograph in screening of 'healthy' populations, the performance of stand-alone AI algorithms was comparable to that of an experienced radiologist, with sensitivity, specificity, positive predicted value, negative predicted value and false-positive rates of 83%, 97%, 1.3%, 100% and 3.0%, respectively.[18]

A consensus statement was developed to determine a standardised lung cancer screening algorithm using AI in Malaysia, based on currently available evidence. Practical considerations and potential limitations with implementing such an algorithm are also discussed.

MATERIALS AND METHODS

This consensus statement was formulated by a multidisciplinary panel of five experts of primary care and specialist doctors via virtual meetings held in March-April 2023. The multidisciplinary panel consists of one cardiothoracic surgeon, one respiratory physician, one radiologist, one oncologist and one general practitioner, all with significant experience in diagnosing, staging and treating lung cancer, both in the public and private healthcare sectors in Malaysia. Four panel experts are members of the Lung Cancer Network Malaysia (LCNM), a not-for-profit non-governmental, disease-centric organisation dedicated to addressing all aspects of lung cancer care here, including preventative (tobacco control) strategies, screening of high-risk individuals, diagnosis, staging and treatment. The consensus findings agreed upon by the panel experts are supported by published evidence. Relevant articles in English published up to February 2023 were considered and reviewed. Finally, a lung cancer screening algorithm is proposed for implementation locally.

RESULTS AND DISCUSSION

Current Landscape in Lung Cancer Screening

LDCT is a non-contrast procedure recommended as part of lung cancer screening in individuals considered at risk of lung cancer.[10] While large randomised trials have demonstrated the utility of LDCT screening in reducing lung cancer-related mortality in high-risk individuals,[12,13], a Malaysian, government-driven effort to evaluate the feasibility and outcomes of using LDCT for lung cancer screening was terminated prematurely due to limited recruitment.[6] Proposed reasons for the failure of the program included a lack of awareness, stigma, fatalism and fear of a cancer diagnosis.[6] This phenomenon is not limited to Malaysia, as reluctance towards screening has also been reported in the United States, resulting in low uptake rates (3.3 to 12.5%).[19] More contemporary data from the UK (Lung Screen Uptake Trial) targeting screening of smokers in socioeconomically deprived areas of England reported better uptake rates (53%) highlighting the value of thoughtful added strategies: primary care invitations, pre-notification letters, scheduled appointments and reminders with a second scheduled appointment.[20] Interestingly, uptake was better when the screening offer was framed within a broader 'lung health check' rather than offered solely as a cancer check, and when there was no upfront mention of smoking cessation.[20-22]

Screening is a process and not an isolated test. Financial affordability, not just for the initial diagnostic investigations but any subsequent therapy required, is a real-world concern and an impediment to screening. A report by the Health Technology Assessment Section, Ministry of Health Malaysia substantiated this observation, citing insurance coverage as a

major barrier to LDCT screening in Malaysia.[23] Slightly above half of Malaysians (56.6%) have no private health insurance;[24] without insurance, LDCT proves to be a financial burden for individuals on limited and fixed income.[23] These combined observations may jeopardise the feasibility of using LDCT exclusively for lung cancer screening in the country.

Innovative Screening Procedure Using AI

One possible approach to facilitate the identification of high-risk individuals is to implement a risk-stratification step, upon which clinical recommendations may be made for LDCT screening or monitoring. This risk-stratification step would reduce dependence on unreliable self-reported measures of cigarette consumption as a means to identifying high-risk individuals. It would also address the unmet need of disease detection in non-smokers.

Chest radiography (chest X-ray) has been proposed as an ideal technique for risk stratification, in identifying thoracic nodules—a potential indicator of early lung cancer. It is one of the most commonly-conducted imaging tests in medicine and a staple component of routine diagnostic clinical work. While LDCT is superior to radiography in sensitivity,[13] chest radiography holds clear advantages in terms of ease of access and affordability. In addition, LDCT has been associated with a higher proportion of false positive findings involving invasive diagnostic procedures compared to chest radiography.[25] However, studies have demonstrated that approximately 20% of visible lung cancers are missed at initial chest radiography,[26,27] underscoring the importance of improving diagnostic accuracy by complementing the two screening modalities.

In order to improve chest radiography sensitivity in the first step of screening, incorporation of AI technology is proposed. AI is an umbrella term for technology that includes machine learning and deep learning, which enables machines to mimic human intelligence and consequently have a transforming effect on medicine. It has led to the development of multiple computer-assisted detection techniques, designed to assist radiologists and general physicians in recognising anomalies on chest radiographs.[11] The chest X-ray interpretation tool utilises deep learning algorithms, which can automatically detect and localise abnormalities, including a possible early lung cancer. The deep convolutional neural network has been shown to enhance radiologists' performance in detection of malignant nodules using chest radiographs, across varying levels of clinician experience.[28-30] Several screening initiatives involving AI-assisted chest radiography and LDCT have commenced, including the recent deployment of the Qure.ai software (Mumbai, India) into National Health Service hospitals in the United Kingdom. A multi-centre retrospective study performed in the United States had demonstrated high performance of Qure.ai's algorithm (qXR) in the detection of missed or mislabelled chest radiography findings, with high sensitivity (96%), specificity (100%) and accuracy (96%).[31] Separately, an analysis of over 13,000 chest X-rays demonstrated the superior ability of qXR to study nodules and detect malignant nodules on chest radiography, compared to radiologists. qXR detected nodules with a specificity of 0.90 (ranging from 0.87 to 0.92), sensitivity of 0.99, and AUC ranging from 0.98 to 0.99. Malignant nodules were detected using qXR with a sensitivity ranging from 0.95 to 1.00, specificity from 0.96 to 0.99, and AUC from 0.99 to 1. On the other hand, the sensitivity of radiologists' performance in detecting nodules ranged from 0.74 to 0.76, with a specificity ranging from 0.98 to 0.99. In detecting the malignant nodules, specificity ranged from 0.98 to 0.99, and sensitivity fell between 0.88 and 0.94.[32]

Proposed Alternative Screening Approach Introduced in a Pilot Project

The National Comprehensive Cancer Network guidelines define high-risk individuals as those with a family history of lung cancer, advancing age and significant smoking history (> 20 pack years). Unfortunately, this may mean the non-smoking cohort of lung cancer victims, in which women are greatly over-represented, remain inadvertently neglected. Considering the higher prevalence of females amongst non-smoking patients with lung adenocarcinoma, an update in screening criteria is pressingly needed. The combination of AI-assisted chest radiography and LDCT funnels the right patients for LDCT imaging and captures the typically 'neglected' such as non-smoking females.

A local pilot project was initiated in the Klang Valley from May 2021 until February 2023 by AstraZeneca, LCNM and Qualitas Medical Health Group, which incorporates AI-assisted chest radiography into lung cancer screening in the community. The goal was to evaluate the feasibility of using AI-assisted chest radiography as an objective risk-stratification step to help funnel at-risk individuals for LDCT screening. Chest radiography was introduced as a diagnostic tool to incidentally pick up IPNs in individuals who came forward to their primary care general practitioner (GP) for reasons other than a suspected lung cancer diagnosis. IPNs are defined as non-calcified lung nodules, with solid, part-solid or ground-glass opacities, which, assuming a spherical nodule, have diameters ranging from 7 to 20 mm.[33] Detection of an IPN is a useful indicator of lung malignancy, as the risk for lung cancer ranges between 6 to 65% depending on the size, morphology and attenuation of the IPN, and clinical context.[34]

In the pilot project, AI-assisted chest radiography was performed for individuals visiting primary clinics with presenting symptoms (such as a bothersome cough or chest discomfort), or asymptomatic individuals coming for routine health assessment. Depending on the radiography results, the GPs customised their consultations based on each individual's risk profile. High-risk individuals (i.e. current smokers or ex-smokers aged between 45 to 75 years with at least a 20-pack year tobacco history) with a normal radiograph were recommended annual LDCT screening. This is supported by a study showing improved outcomes in patients who attended LDCT follow-ups, whose cancers were missed at the first screening.[35] On the other hand, GPs referred IPN-detected individuals, regardless of their risk profile, to one of three tertiary specialist hospitals for an LDCT scan to ascertain the presence of an underlying lung malignancy. To date, 16,551 AI-assisted chest radiographs have been conducted in the clinics, with 389 IPNs detected (2.35%). Follow-up of IPN-detected individuals are currently underway to determine the percentage of lung malignancy

Fig. 1: Proposed algorithm for lung cancer screening in Malaysia, with an objective risk-stratification step using AI-assisted chest X-ray where individuals who show IPN detection are counselled to undergo LDCT, suspected lung malignancies are biopsied, and confirmed lung malignancies are staged and treated appropriately (AI: Artificial intelligence, GP: General practitioner, IPN: Indeterminate pulmonary nodule, LDCT: Low-dose computed tomography).

detected from the incidental discovery of an IPN. This is an important pending data gap but preliminary feedback via telephonic survey suggests uptake for the subsequent LDCT imaging was unfortunately, generally poor. Going forward, barriers to screening need to be elucidated and addressed thoughtfully. Nevertheless, this pilot project with AI-assisted screening serves as fertile groundwork for transforming lung cancer screening in Malaysia.

The proposed alternative screening approach takes both cost and practicality into consideration. Presently, a high-risk population-based LDCT lung cancer screening program is less pragmatic. The incorporation of AI-assisted chest radiography as an affordable risk-stratification step is highly relevant as an intermediary diagnostic tool in Malaysia (Fig. 1).

The inclusion of AI-assisted chest radiography in the screening for lung cancer is essential in order to improve the long-term survival of lung cancer patients, by setting stage shift as an endpoint for cancer screening. Detection of early lung cancer which is more amenable to curative treatment will not only translate into enhanced patient survival, but is also more cost-effective in the long run. Our preliminary experience with AI-enabled chest X-rays (qXR [Qure.ai]) suggests the software is easy to use, affordable and scalable. Feedback from our colleagues in general practice was most favourable. Our colleagues had found the whole process to be user-friendly and felt empowered to swiftly decide on the next course of action. Patients, too, were similarly highly satisfied to receive a detailed report in minutes, and medical advice at a single consultation. Failure to adopt and appropriately utilise such technology may be a significant missed opportunity for Malaysia.

Requirements for Screening Centre and Equipment

The implementation and effective conduct of AI-assisted chest radiography requires the expertise of a multidisciplinary team (MDT) comprising a radiologist, oncologist, pulmonologist, pathologist, thoracic surgeon, nurse and a co-ordinator experienced in the diagnosis and treatment of lung cancer and in programmes pertaining to it. It is imperative for screening centres to be certified according to a standardised methodology. Continued education of the staff and site accreditation also contribute to the effectiveness of a screening programme. A registry is also desired to keep track of screening statistics and outcomes. Information on equipment specifications and radiographic settings/protocol should also be elucidated and made easily accessible for clinicians' reference. Informed consent of patients undergoing screening must include salient information on accuracy of the screening program, such as biopsy rates. Patients should also have access to tertiary specialist centres with a dedicated multidisciplinary team to support the investigation of a detected pulmonary nodule.

Expected Outcomes with AI-assisted Chest Radiography

Among the goals of lung cancer screening with a risk-

stratification step using AI-assisted chest radiography are to increase the uptake of screening amongst the public, and to improve outreach to otherwise-unscreened low-risk populations (particularly non-smokers and females). Screening is anticipated to bring forward the stage distribution at diagnosis, early detection improves survival and reduces the risk of mortality due to late treatment.[36-38] We anticipate that a stage shift in cancer detection will enhance the possibility of successful curative treatment, as well as reduce attending side effects associated with long-term or multiple lines of treatment. By extension, overall treatment cost is expected to reduce.

Chest radiography is a widely known and well-accepted investigation by the public. Implementation of an affordable and easily accessible screening modality for lung cancer is anticipated to increase public awareness of and participation in lung cancer screening efforts locally. Additionally, screening provides a timely opportunity to educate individuals regarding the risks of smoking, thus, education should be carefully integrated into the screening process to encourage and support smoking cessation.

Potential Limitations in Implementing an AI-assisted Lung Cancer Screening Programme

AI-assisted medical imaging for screening has gained an important role in supporting efficient and quick clinical decision-making. However, there are a number of potential limitations pertaining to the implementation of AI-assisted lung cancer screening. Firstly, the attitude of both clinicians and patients to the adoption of AI can be mixed and unpredictable. In general, radiologists have been optimistic on the whole about the potential of AI, but many understandably still harbour concerns that the technology may disrupt or undermine their professional reputation or livelihood. Hence, there is a need to educate all stakeholders to address concerns and allay anxieties. Another challenge impeding clinical implementation of AI-assisted screening is reproducibility, due to various differences in the image acquisition protocols between different studies and research institutions. These differences can affect the signal-to-noise ratio and the characteristics of extracted images. Consequently, variations in imaging features between patients may be due to acquisition parameters, rather than biological. This limitation could be addressed through the exclusion of features strongly influenced by acquisition parameters, or through standardising image acquisition by using open imaging protocols.

Technical integration is also a significant setback for implementation of AI software into routine radiology practice. Computational power required for advanced AI algorithms may exceed local capabilities, and this may drastically slow down scanner performance. This could be overcome with cloud-based solutions like our software, although this may be accompanied with its associated concerns, such as data security and privacy, and internet performance. In addition, regular updates over the lifecycle of an AI system is to be expected.

One of the concerns with lung cancer screening is that a subset of smokers might use a seemingly normal result as an excuse to continue smoking, although current evidence on this is limited. Vigorous and sustained smoking cessation efforts must accompany lung cancer screening for current smokers. Our preliminary experience with AI-chest radiography imaging as a triage or prelude to definitive LDCT screening of an IPN is promising, with a diagnostic rate of approximately 2.5% in a local urban population. Primary care is fast shifting from symptom-based therapy to preventative and predictive or pre-emptive care. Feedback from our primary care colleagues suggests that this technology is a potential game-changer as it is simple and swift to utilise, generates a high-quality image and detailed radiology report within minutes, thereby empowering the general practitioner immediately on the next course of action. The benefits of enhanced diagnostic accuracy, a shorter turnaround time and ease of use are obvious and immense. The follow-up of patients with IPNs, however, has been challenging, in part due to the fact that the project was conducted throughout the coronavirus disease 2019 (COVID-19) pandemic and thus was hampered by travel restrictions, periods of quarantine and the stigma of both diseases. Furthermore, well-established barriers to screening, including an understandable fear of a possible cancer diagnosis, fatalism, poor health literacy and high financial cost, remain. Going forward, we have sought to mitigate this with free screenings and use of patient navigators.

CONCLUSION

Lung cancer remains a leading cancer and cancer-killer in Malaysia, with the worst reported 5-year survival of all the major solid tumours.[2-5] A preponderance of late-stage presentation is to blame and is likely to worsen in the coming years due to recent COVID-19 disruptions. Despite tremendous advances in the diagnostic and treatment landscape for lung cancer (namely genomic molecular profiling and next generation sequencing, as well as emergence of novel bespoke therapies such as systemic immunotherapy and oral targeted therapies), detection of more early-stage disease via impactful screening coupled with effective tobacco control is imperative to save more lives. This consensus statement addresses the need to 'widen the net' for early and widespread screening of lung cancer to facilitate effective cancer control in our country. The combined staged strategy of AI-assisted chest radiography and complementary LDCT imaging has great potential in detecting early-stage lung cancer in a timely manner, and irrespective of risk status. The proposed screening algorithm provides a guide for clinicians in Malaysia to participate in screening efforts. Active lung cancer screening enables stage shift towards detection of more early-stage disease, which is more effective and economical to treat, in addition to better prognosis in terms of both patient survival and quality of life.

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High-dose pulse methylprednisolone vs. dexamethasone standard therapy for severe and critical COVID-19 pneumonia: Efficacy assessment in a retrospective single-centre experience from Malaysia

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ABSTRACT

Introduction: The use of dexamethasone (DXM) has been associated with decreased mortality in the patients with hypoxemia during the coronavirus disease-2019 (COVID-19) pandemic, while the outcomes with methylprednisolone (MTP) have been mixed. This real-life study aimed to evaluate the outcomes of patients with severe respiratory failure due to COVID-19 who were treated with high doses of MTP.

Materials and Methods: This retrospective cohort study enrolled hospitalised patients between May 2021 and August 2021, aged 18 years and above, with severe respiratory failure defined by a ratio of oxygen saturation to fraction of inspired oxygen (SF ratio) of less than 235. The treatment protocol involved administering high-dose MTP for 3 days, followed by DXM, and the outcomes were compared with those of patients who received DXM alone (total treatment duration of 10 days for both groups).

Results: A total of 99 patients were enrolled, with 79 (79.8%) receiving pulse MTP therapy and 20 (20.2%) being treated with DXM only. The SF ratio significantly improved from a mean of 144.49 (±45.16) at baseline to 208 (±85.19) at 72 hours ($p < 0.05$), with a mean difference of 63.51 ($p < 0.001$) in patients who received ≤750 mg of MTP. Additionally, in patients who received >750 mg of MTP, the SF ratio improved from a baseline mean of 130.39 (±34.53) to 208.44 (±86.61) at 72 hours ($p < 0.05$), with a mean difference of 78.05 ($p = 0.001$). In contrast, patients who received DXM only demonstrated an SF ratio of 132.85 (±44.1) at baseline, which changed minimally to 133.35 (±44.4) at 72 hours ($p = 0.33$), with a mean difference of 0.50 ($p = 0.972$). The incidence of nosocomial infection was higher in the MTP group compared with the DXM group (40.5% vs. 35%, $p = 0.653$), with a relative risk of 1.16 (95% CI: 0.60-2.23).

Conclusion: MTP did not demonstrate a significant reduction in intubation or intensive care unit admissions. Although a high dose of MTP improved gas exchange in patients with severe and critical COVID-19, it did not provide an overall mortality benefit compared to standard treatment.

KEYWORDS:
COVID-19; acute respiratory distress syndrome; respiratory failure; pneumonia; corticosteroids

INTRODUCTION

The year 2019 witnessed a significant milestone with the emergence of the novel coronavirus disease 2019 (COVID-19), which rapidly spread worldwide, leading to a global pandemic. COVID-19 patients can range from being asymptomatic to exhibiting varying degrees of symptoms, including mild to severe manifestations. The cytokine release syndrome triggered by COVID-19 results in a robust inflammatory response, potentially leading to severe organ dysfunction.[1] Among the severe cases, respiratory failure and the subsequent need for oxygenation support are common. Acute respiratory distress syndrome (ARDS) represents the most critical form of respiratory failure observed in the clinical spectrum of COVID-19 pneumonia, often necessitating mechanical ventilation and admission to the intensive care unit (ICU).[2]

Dexamethasone (DXM) has emerged as the preferred treatment for hypoxemic COVID-19 patients following the remarkable findings of the RECOVERY trial. This trial demonstrated improved mortality outcomes in mechanically ventilated COVID-19 patients receiving DXM (6 mg once daily for 10 days) compared to standard care.[3] Alongside DXM, the role of other systemic corticosteroids, particularly methylprednisolone (MTP), has been investigated in several small-scale clinical trials.[4-7] While these studies have provided some evidence supporting the use of MTP, the overall benefit of MTP over DXM remains uncertain and controversial. Therefore, this retrospective study aims to evaluate the clinical outcomes of patients with severe respiratory failure due to COVID-19 who received MTP compared to DXM.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the University of Malaya Medical Center in Malaysia from May 2021 to August 2021. The study enrolled hospitalised patients

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Table I: Sociodemographic and clinical characteristics of patients with severe and critical COVID-19 infection

	MTP (n=79)	DXM (n=20)	p value
Age (years)	57.5 (12.2)	62.9 (11.9)	p=0.04
Gender			
Male	47 (59.5)	12 (60.0)	p=0.48
Female	32 (40.5)	8 (40.0)	
Comorbidities			
HPT	55 (69.6)	10 (50.0)	p=0.05
DM	49 (62.0)	8 (40.0)	p=0.03
Stroke	3 (3.8)	1 (5.0)	p=0.40
Heart disease	14 (17.7)	2 (10.0)	p=0.20
Lung disease	3 (3.8)	1 (5.0)	p=0.40
Renal disease	9 (11.4)	1 (5.0)	p=0.20
Malignancy	2 (2.5)	0 (0.0)	p=0.25
COVID Category			
4	58 (73.4)	14 (70.0)	p=0.38
5	21 (26.6)	6 (30.0)	
Day of illness, median (IQR)	4 (2-7)	4 (3-6)	p=0.45
Laboratory results on admission			
Pre-Treatment			
WBC	11.12 (4.9)	9.76 (4.5)	p=0.125
ALC	1.11 (2.1)	1.11 (0.4)	p=0.494
CRP	185.73 (109.9)	108.69 (198.8)	p=0.013
Ferritin	1630.39(1181.1)	1569.24(1409.5)	p=0.431
SF ratio on admission	141 (43.17)	132 (44.17)	p = 0.44
ICU*	50 (63.3)	1 (5.0)	
MV**	18 (22.8)	4 (20.0)	
Cumulative steroid dose, median (IQR)	192 (146-313)	66 (48-81)	p<0.05
Cumulative dose MTP			
≤750mg	61 (77.2)		
>750mg	18 (22.8)		
Other medication			
Faviparavir	23 (29.1)	2 (10.0)	p=0.079
Tocilizumab	28 (35.4)	8 (40.0)	p=0.710
Baricitinib	16 (20.3)	6 (30.0)	p=0.349

Abbreviation: WBC: white blood count, ALC: absolute lymphocytes count, CRP: C-reactive protein, ICU: intensive care unit, MV: mechanical ventilation, IQR = interquartile range.
Data are presented as n (%) or mean ± standard deviation unless otherwise stated.
*Patients admitted to ICU prior treatment , **Patients were on mechanical ventilation prior treatment

aged 18 years and above who were diagnosed with category 4 and 5 COVID-19 infection. The severity of patients was categorised according to local guidelines.[8] Patients requiring oxygenation support were classified as severe (category 4), while critically ill patients were further subcategorised as 5a and 5b. Category 5a patients required non-invasive ventilation or high-flow nasal cannula therapy, while category 5b patients were intubated and received mechanical ventilation support. The severity of respiratory failure was determined by the ratio of oxygen saturation (SpO2) to the fraction of inspired oxygen (FiO2) known as the SF ratio. The correlation of the SF ratio with the partial pressure of oxygen in arterial blood (PaO2)/FiO2 (PF ratio) for assessing gas exchange in ARDS has been previously studied and recognised.[9] In this study, patients with COVID-19 having a SF ratio of <235 (correlating with a PF ratio of <200) were included. Patients with COVID-19 infection below category 4 who were treated with MTP or DXM for reasons other than COVID-19 were excluded from the study. All medical data were obtained from electronic medical records and recorded in a Microsoft Excel spreadsheet.

The patients were divided into two groups based on the treatment received. The first group consisted of patients who received pulse MTP for 3 days followed by DXM, while the second group received DXM alone. The total duration of corticosteroid therapy for both groups was 10 days. The decision regarding the dosage of MTP was based on the managing physician's clinical judgment. Patients in the first group were further categorised into those who received a lower cumulative dose (≤ 750 mg) and those who received a higher cumulative dose (> 750 mg) of MTP. Patient demographics, medical comorbidities, laboratory parameters, treatment response, complications, length of stay and overall mortality rates were analysed. This retrospective review was approved by the Institutional Ethics Board (MREC ID NO: 2021818-10486), and informed consent was waived.

Statistical Analysis

IBM Statistical Package for the Social Sciences for Macintosh (Version 26.0, Armonk, NY: IBM Corp) was used for statistical analysis. Continuous variables with normal distribution were presented with a mean (standard deviation). Non-normally distributed variables were reported as median (interquartile range [IQR]). The results were compared using the student T-test and Wilcoxon signed-rank test. P values were two-sided with a statistical significance value of <0.05. A minimum sample size of 82 is required to achieve a power of 80% using a power calculator with a two-tailed test, α power of 0.05 and p-value of 5% for statistical significance.

Table II: Gas exchange and laboratory results of patients pre and post treatment

	Pre Treatment SF ratio	Post Treatment (72 hours) SF ratio	p value	Mean difference
Gas exchange				
MTP (Dose ≤ 750mg)	144.49 (45.16)	208 (85.19)	p < 0.05	63.51 p<0.001
MTP (Dose > 750mg)	130.39 (34.53)	208.44 (86.61)	p< 0.05	78.05 p=0.001
DXM	132.85 (44.17)	133.35 (44.40)	p=0.33	0.50 p=0.972
Laboratory results				
MTP	WBC : 11.12 (4.9)	WBC : 13.75 (6.1)	0.002	
	ALC : 1.11 (2.1)	ALC : 1.30 (2.1)	0.260	
	CRP : 108.69 (198.8)	CRP : 56.5 (74.1)	0.018	
	Ferritin : 1569.24 (1409.5)	Ferritin : 1443.7 (1440.9)	0.297	
DXM	WBC : 9.76 (4.5)	WBC : 12.83 (5.4)	0.081	
	ALC : 1.11 (0.4)	ALC : 1.25 (0.6)	0.295	
	CRP : 115.73 (109.9)	CRP : 63.94 (62.9)	0.046	
	Ferritin : 1630.39 (1181.1)	Ferritin : 1055.85 (624.3)	0.071	

Abbreviation: MTP: methylprednisolone, DXM: dexamethasone. WBC: white blood count, ALC: absolute lymphocytes count, CRP: C-reactive protein. Data are presented as mean ± standard deviation.

Table III: Outcome of patients

	MTP (n=79)	DXM (n=20)	p value	Mean difference
ICU*	4 (5.1)	1 (5.0)	p = 0.34	
MV**	15 (19.0)	2 (10.0)	p = 0.30	
Patients developed nosocomial infection	32 (40.5)	7 (35.0)	p=0.653	
Overall length of stay	19.35 (± 11.4)	11.95 (±6.0)	p=0.057	-7.40 (p=0.006)
Discharge	42 (53)	10 (50)	p=0.064	
Death	37 (47)	10 (50)		

Abbreviation: ICU: intensive care unit, MV: mechanical ventilation,
Data are presented as n (%) or mean ± standard deviation.
* Patients admitted to ICU after 72 hours , ** Patients intubated after 72 hours

RESULTS

This study enrolled a total of 99 patients with severe and critical COVID-19 infection, with 79 (79.8%) receiving pulse MTP therapy and 20 (20.2%) being treated with DXM alone. Nearly two-thirds of patients in both groups had category 4 severity according to the classification system. The median duration of illness at hospital presentation was 4 days for both groups. The baseline demographics and clinical characteristics of the patients are presented in Table I. Upon admission, 50 (63.3%) patients in the MTP group received treatment in the intensive care unit (ICU), and among these patients, 22.8% required mechanical ventilation. Four (20%) mechanically ventilated patients received DXM only. The mean SF ratio for patients in the MTP group compared to the DXM group was 141 (±43.17) versus 132 (±44.17) (p = 0.44).

A cumulative MTP dose of ≤750 mg was administered to 61 (77.2%) patients, while 18 patients (22.8%) received >750 mg of MTP for a duration of 3 days. The maximum recorded cumulative MTP dose in the >750 mg group was 1500 mg, given to two patients. Significant improvement in the SF ratio was observed 72 hours after treatment in the MTP group. The SF ratio at baseline was 144.49 (±45.16) and increased to 208 (±85.19) at 72 hours (p < 0.05), a mean difference of 63.51 (p < 0.001) (Fig. 1) for patients receiving ≤ 750 mg of MTP, whereas for those receiving >750 mg, the SF ratio at baseline was 130.39 (±34.53) and increased to 208.44 (±86.61) at 72 hours (p < 0.05), with a mean difference of 78.05 (p = 0.001) (Fig. 1). In contrast, patients who received DXM only showed an SF ratio of 132.85 (±44.1) at baseline and 133.35 (±44.4) at 72 hours post-treatment (p = 0.33), with a mean difference of 0.50 (p = 0.972) (Fig. 2). The changes in gas exchange parameters from pre-treatment to 72 hours post-treatment are summarised in Table II. Notably, there was an improvement in C-reactive protein (CRP) levels at 72 hours post-treatment in both treatment groups. A comparison of laboratory parameters between the two groups at baseline and 72 hours post-treatment is provided in Table II.

Following MTP therapy, 15 patients experienced deterioration in their condition, necessitating mechanical ventilation. Additionally, four patients required admission to the intensive care unit (ICU) for close monitoring. In the DXM-only group, two patients (10%) required mechanical ventilation, and one patient was transferred to the ICU for specialised care. The incidence of nosocomial infections was higher but did not achieved statistically significance among patients treated with MTP compared to those receiving DXM alone (40.5% vs. 35%, p = 0.653). The relative risk of developing nosocomial infection from the use of MTP was 1.16 (95% CI: 0.60-2.23). The duration of hospital stay was longer in the MTP group (19.35 [± 11.4] days) compared to the DXM group (11.95 [± 6.0] days), with a p-value of 0.057. While the mortality rate was slightly lower in the MTP-treated

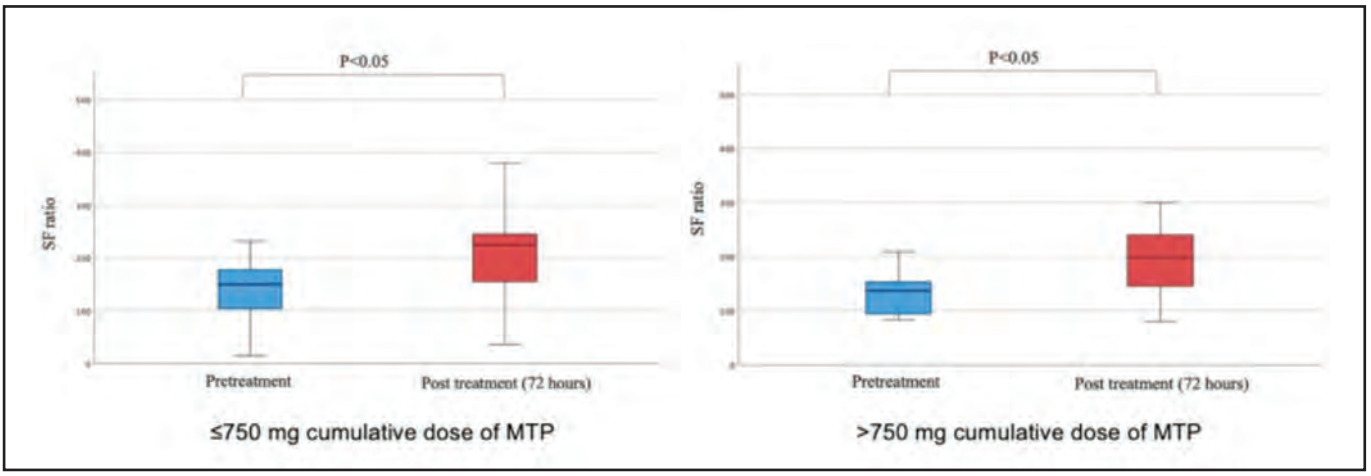

Fig. 1: SF ratio for patients treated with MTP.

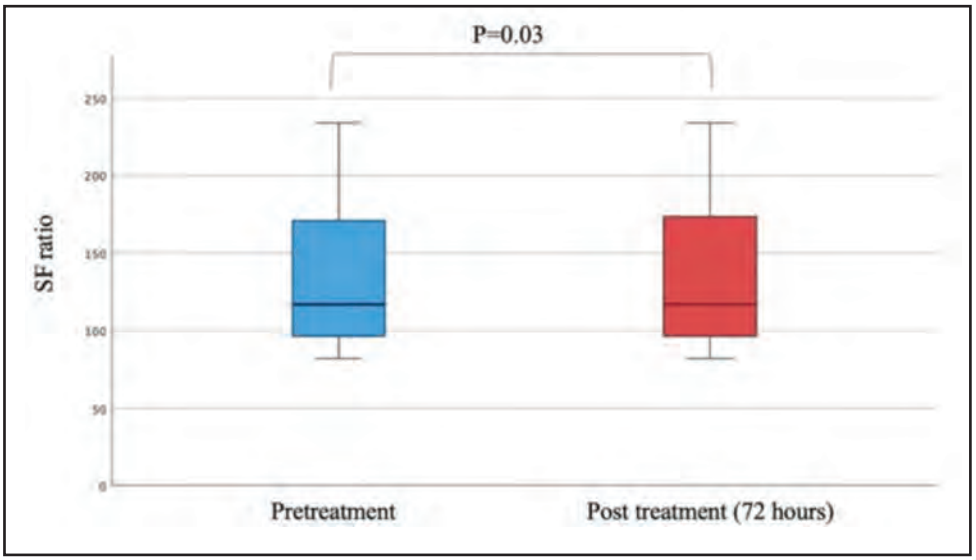

Fig. 2: SF ratio for patients who received only DXM.

group compared to the DXM group (47% vs. 50%), this difference did not reach statistical significance, with a relative risk of 0.94 (95% CI: 0.57-1.54). Detailed information on these outcomes is presented in Table III.

DISCUSSION

The spectrum of COVID-19 infection ranges from mild to severe. Approximately 20% of patients experience a severe illness that necessitates oxygen support, with 5% of these patients classified as being in the critical stage, presenting with respiratory or multi-organ dysfunction.[10] The incidence of severe to critical COVID-19 infection was high prior to widespread vaccination. Multiple treatment options, such as specific antiviral therapy and immunomodulators, have been investigated, however, none have demonstrated effectiveness against severe acute respiratory syndrome coronavirus 2.

The primary challenge posed by severe COVID-19 infection arises when patients develop ARDS and cytokine release syndrome. Numerous cytokines, including tumour necrosis factor-alpha, interleukin (IL)-1B, IL-2 IL-6, IL-8, IL-10 and interferon y, contribute to profound systemic inflammation, leading to significant morbidity and mortality.[11] The use of glucocorticoids gained momentum due to their potent anti-inflammatory action, targeting a multitude of pro-inflammatory genes implicated in cytokine storms.[12-13] In patients with hypoxemic COVID-19, administration of DXM at a daily dose of 6 mg for up to 10 days resulted in reduced mortality rates within 28 days compared to standard care (rate ratio 0.83; 95% confidence interval [CI]: 0.74–0.92; $p < 0.001$), as demonstrated in the pivotal RECOVERY trial.[3] Furthermore, the recent multicentre randomised placebo-controlled study by Villar et al. provided insights into the long-standing controversy surrounding corticosteroid use in patients with ARDS. The study revealed that patients with moderate to severe ARDS who received DXM had fewer days

of mechanical ventilation and lower overall mortality rates.[14] Glucocorticoids are frequently prescribed for a wide range of medical conditions. However, the selection of the appropriate glucocorticoid is not a one-size-fits-all approach due to their diverse pharmacological properties. MTP, an intermediate-acting glucocorticoid, exhibits superior lung penetration compared to other available options.[15] Consequently, MTP may serve as a more effective anti-inflammatory agent during the pulmonary phase of severe COVID-19 infection, reducing lung injury while minimising undesired side effects associated with prolonged corticosteroid exposure, thanks to its shorter plasma and biological half-life compared to DXM.[16-17]

The prudent use of MTP, a potent glucocorticoid, and higher doses equivalent to DXM is recommended for patients with severe to critical COVID-19 presenting with cytokine storm and ARDS. Achieving therapeutic plasma levels and optimal saturation of glucocorticoid receptors to elicit sufficient anti-inflammatory effects necessitate higher initial loading and subsequent maintenance doses.[18] The efficacy of MTP administration was initially observed in an early retrospective study conducted in Wuhan, China, during the initial phase of the COVID-19 pandemic. Low to medium doses of MTP (25–80 mg/d) were found to prevent disease progression to a severe or critical state in patients aged ≤65 years with COVID-19.[19] Subsequent studies further supported the use of MTP.[5,7] A triple-blinded randomised controlled trial demonstrated that patients treated with MTP exhibited improved clinical status, as measured by the World Health Organization Ordinal Scale for Clinical Improvement (3.909 vs. 4.873, p =0.004), and had a lower requirement for mechanical ventilation (18.2% vs. 38.1%, p=0.040) compared to those treated with DXM.[5] Patients with severe ventilatory failure due to COVID-19 showed more significant improvement in gas exchange when treated with MTP compared to DXM. Similar findings were observed with the administration of MTP at doses of 125–250 mg/d for three consecutive days during the second week of illness in patients with severe disease and elevated inflammatory markers.[6] Both cohorts of patients, particularly those treated with MTP, exhibited improvements in blood inflammatory markers such as CRP and ferritin. Additionally, a cohort study by Pinzón MA et al. reported a significant reduction in CRP, D-dimer, and lactate dehydrogenase values in 216 patients treated with MTP.[7]

The current study demonstrated improvement in gas exchange at 72 hours with the use of MTP. Significant gas exchange improvement was seen even with the smaller cumulative dose of MTP of ≤750 mg. However, despite gas exchange improvement at 72 hours, patients treated with MTP remained in severe respiratory failure with a mean SF ratio of < 235. Hence, we were unable to demonstrate that the use of MTP reduced intubations or ICU admissions in a cohort of severely and critically ill COVID-19 patients with respiratory failure. One of the concern associated with high doses of corticosteroids is the potential risk of secondary infection. The risk of nosocomial infection is undeniably increased with the injudicious use of glucocorticoids although the rate of nosocomial infection for both groups of patients in this study was not statistically different. Similarly, clinicians are reminded that pulse glucocorticoids used in the treatment of many life-threatening autoimmune diseases are associated with an increased risk of infection.[17]

In terms of mortality, the Cruces COVID Study Group reported that MTP at week 2 of disease showed a lower adjusted risk of death and death or intubation.[6] Current study demonstrated no mortality benefit at 28 days with the use of high-dose MTP for severe and critically ill patients. The disparity in results may be explained by patient selection. Patients recruited in this study demonstrated more severe ventilatory failure (overall SF ratio of 141.28 [±43.17]) compared to those reported in the previous study (median SF ratio 380 [160] and overall PF 255 [240–271]).[6-7] Thus, improvement in short-term gas exchange may not translate into overall mortality benefits in patients with severe or critical COVID-19. The findings of our study are in line with those reported by Ngu et al.,[20] although our patient cohort exhibited more severe respiratory failure. This definitive evidence confirms the limited role of high-dose MTP in the management of severe and critically ill patients with COVID-19 pneumonia.

Some limitations identified in the current study include its single-centre and retrospective nature, which can introduce selection bias. The number of patients recruited is limited. The MTP prescription solely based on the physician's clinical judgment might contribute to indication bias. Additionally, heterogeneity in the overall management was anticipated during the height of the pandemic when medical resources were overwhelmed.

CONCLUSION

The use of high-dose methylprednisolone (MTP) in patients with severe or critically ill COVID-19 and severe ventilatory failure may offer short-term improvement in gas exchange but is not associated with improved clinical outcomes. There was no observed mortality benefit compared to standard treatment. However, considering a lower dose of MTP may be a reasonable therapeutic approach for the patients with COVID-19 experiencing mild to moderate ventilatory failure. To validate these findings, larger randomised trials are required.

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Correlation between impulse oscillometry with bronchodilator reversibility in asthmatic population in a tertiary referral centre

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ABSTRACT

Introduction: Spirometry is considered as a 'gold standard' for diagnosis of asthma. Impulse oscillometry (IOS) is an alternative diagnostic tool which requires less cooperation by the participants. We performed a study to determine the correlation of IOS with bronchodilator reversibility from spirometry in asthmatic participants. We studied the correlation between forced expiratory flow ($FEF_{25\%–75\%}$) and differences between the resistance at 5Hz and 20Hz ($R_5–R_{20}$) in small airway disease (SAD) and the proportion of SAD diagnosed using IOS.

Materials and Methods: This was a cross-sectional study involving 82 asthmatic participants in Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia (UKM) conducted between December 2020 till January 2022. Participants performed pre- and post-bronchodilator IOS and spirometry within the same day. Correlation between spirometry and IOS parameters and $FEF_{25\%–75\%}$ with IOS were determined and analysed.

Results: The change of forced expiratory volume in 1 second (FEV_1) was statistically correlated with a change of R5 in IOS. A decrement of 14.5% in R5 can be correlated with positive bronchodilator response (BDR) with a sensitivity of 63.9% and specificity of 60.9%, p=0.007. Pre-bronchodilator $FEF_{25\%–75\%}$ correlated with all parameters of SAD in IOS, e.g., R_5-R_{20}, reactance at 5Hz (X_5) and area of reactance (AX), p < 0.05. IOS detection for SAD is higher compared to $FEF_{25\%–75\%}$ in the BDR negative group (91.3% vs 58.7%).

Conclusion: IOS detected both bronchodilator reversibility and SAD hence can be considered as an alternative tool to spirometry for diagnosis of asthma in adults. IOS detected SAD more than $FEF_{25\%–75\%}$, especially in BDR-negative group.

KEYWORDS:
asthma; impulse oscillometry; bronchodilator reversibility; small airway disease; spirometry

INTRODUCTION

Asthma is a chronic inflammatory airway disease affecting large and small airways.[1,2] Asthma affects approximately 339 million people worldwide, and the prevalence of asthma among the Malaysian adult population was reported as high as 6.4% based on National Health and Morbidity Survey 2011.[3,4]

Typical asthma symptoms include wheezing, shortness of breath, chest tightness and coughing.[1,5] Spirometry is an important tool used to demonstrate variable expiratory airflow limitation to confirm the diagnosis of asthma.[1] It measures the amount of air that is expelled from a patient. A good spirometry manoeuvre requires a good expiratory effort, cooperation from the patient and trained personnel to coach the patient.[6] Although spirometry is reproducible, non-invasive and sensitive to changes in airflow obstruction, the actual manoeuvre can have many errors which may affect the results.

When performing spirometry, it is necessary to achieve acceptable quality. The patient must perform the test with maximal inspiration and expiration without hesitation with a back-extrapolation volume of <0.15 L. There must be strictly no cough or cessation of airflow during the manoeuvre. The manoeuvres should meet the end of test criteria defined by exhalation of more than 6 seconds with less than 0.025 L being exhaled in the last 2 seconds or a plateau of at least 1 second.6 Spirometry typically shows an obstructive pattern in participants with asthma, defined by an FEV_1/FVC ratio of less than 0.7.

Impulse oscillometry (IOS) is a useful tool as an alternative to spirometry.[7,8] It is a non-invasive test requiring minimal cooperation from the patient. It is effort independent and is especially useful in both young children and elderly participants.

It is relatively easy to perform. Participants are seated during the procedure. A nasal clip is attached, and tight seal is applied between the mouthpiece and lips to prevent air leak. Participants perform normal tidal breathing during the procedure for about 30 seconds. Around 120–150 sound impulses are transmitted into the lungs, resulting in informative parameters for the interpretation.[9]

IOS indicates the respiratory system impedance (Zrs). Impedance is based on resistance (Rrs) and reactance (Xrs) of the respiratory system. Rrs is the energy required to pass through the whole airway, including large and small airways, to distend the lung. Resistance at 5Hz (R_5) is an index affected by large and small airways. Resistance at 20Hz

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(R_{20}) indicates an index of resistance of large airways. Differences between R_{20} and R_5 show the resistance of small peripheral airways. Resistance is independent of oscillation frequency in a healthy person. R_5 is increased whenever central or peripheral airways obstruction occurs. Central airway obstruction increases Rrs evenly independent of oscillation frequency; however, in peripheral airway obstruction, Rrs is elevated at low frequency; thus, it becomes frequency-dependent. Xrs is composed of forces of the moving air column named as inertance (I) and the elastic properties of the lung called capacitance (C).

Both Rrs and Xrs are measured in cmH2O L^{-1} s^{-1} or kPa L^{-1} s^{-1}. At lower frequencies, the elastic properties of the lung (C) are dominant, but at the higher frequency, the inertive pressure of the large airway takes place. The reactance at 5Hz (X_5) indicates the combined effect of inertance and capacitance of the lung; however, the elastic properties of the lung are dominant. In other words, X_5 indicates the elastic recoil of the peripheral airways. The reactance (AX) area is the area under the curve between the reactance values for 5Hz and resonance frequency. AX reflects the changes in the degree of peripheral airway obstruction.[9]

Early detection of small airway disease (SAD) is crucial, especially for individuals with preserved pulmonary function. In a observational cohort study performed, 91% of asthmatic patients have SAD after undergoing various test; and SAD is associated with future risk of exacerbations.[10] Another study showed that SAD is associated with poor asthma control despite FEV_1 within normal range.[11] It is proven that early treatment for this category of participants can improve the long-term outcome and reduce exacerbation in the future.[9,12]

In spirometry, forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%–75\%}$) is used to detect the SAD, but this value is highly dependent on forced vital capacity (FVC).[13]

$FEF_{25\%–75\%}$ is routinely obtained during spirometry. It is used as a measurement of distal airways calibre. It is reported to be more sensitive in reflecting airway hyperresponsiveness than FEV_1 in asthmatic participants. Therefore, the impairment of $FEF_{25\%–75\%}$, which is defined by < 65%, especially in those participants with normal FEV_1 may indicate the presence of SAD in asthma.[9]

IOS can be an alternative tool for the detection of SAD. Studies also show that IOS can detect small airway problems better than spirometry.[9-10,13] It is particularly important as bronchial asthma affects the small airway.[9,10]

However, IOS faces limited global and Malaysian adoption as a spirometry substitute due to several factors. Firstly, spirometry is well-established, cost-effective, and universally accepted, making a shift challenging. Additionally, standardisation issues and lack of extensive normative data for IOS hinder its widespread use. Training requirements for technicians and physicians may contribute to the reluctance in adopting IOS, as it demands specialised knowledge. Economic constraints in some regions, including Malaysia, may also impede the integration of IOS into routine respiratory assessments.

Overall, a combination of historical prevalence, standardisation concerns and economic considerations collectively limits the global and Malaysian embrace of IOS over spirometry.

A study done mainly on children showed accuracy in diagnosing bronchial asthma.[14] IOS parameters have also been found to be a better tool for evaluating asthma control compared to the usage of spirometry.[15] Palacios et al. did a study on 142 adult asthmatic participants and showed that IOS values had a good association with spirometry values. Thus, IOS could be considered an alternative tool to spirometry. However, IOS could not classify the participants based on the degree of asthma control.[12] Another study was done by Park et al. also showed that IOS may play a role in diagnosing airway obstruction and bronchodilation in adult asthmatic participants. This study, however, demonstrated the discrepancies between spirometry values and respiratory resistance from IOS.[16]

The correlation between IOS and spirometry in asthma has not yet become a standard method for assessing lung function, especially in adults. IOS should be considered another useful tool for detecting SAD. More studies and data are required to interpret IOS parameters to be implanted in clinical practice in the future for better asthma control in the population.

Hence, our study's primary objective was to determine the correlation between IOS and bronchodilator reversibility in the asthmatic population. Our secondary objective was to study the correlation of $FEF_{25\%–75\%}$ and differences between R_5 and R_{20} (R_5-R_{20}) in peripheral airway disease and the proportion of SAD in asthmatic participants using IOS.

MATERIALS AND METHODS

Study Design:

A cross-sectional study of outpatient asthmatic participants was done in HCTM, UKM between December 2020 and January 2022. This study was approved by the Research Ethics Committee, UKM, FF-2020-291. Participants attending the outpatient clinic were screened.

We included the following participants: age 18 years and above with physician diagnosis of asthma, non-smokers, or ex-smokers who had smoked < 5 pack-years but had not smoked for > 1 year.

Participants were excluded if they were current smokers, had a recent exacerbation of asthma requiring oral steroids and/or hospitalisation within the last 1 month, diagnosed with other respiratory diseases, and pregnancy. Participants who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with reverse-transcriptase-polymerase chain reaction (RT-PCR) within 48 hours before recruitment were also excluded. Participants were included in the study after informed consent was provided.

Sample size was calculated based on the intended primary objective of determining the correlation between IOS with bronchodilator reversibility in the asthmatic population in HCTM, UKM. With 95% confidence level and 80% power for

different area under curve (AUC = 0.76)[17] and effects (δ = 0.1), the sample required was 156.

Procedure

The demographic data, including age and gender were recorded. Participants completed the self-administered survey, Asthma Control Test (ACT) in either English or Malay language depending on the subject's preference.

Participants were required to answer 5 five questions based on day-night time symptoms, rescue bronchodilators, and daily activities.[4] An ACT score of 19 or less was defined as not well-controlled asthma, while a score of 20 or more was defined as controlled asthma.[4]

All participants were required to perform a COVID-19 RT-PCR test 48 hours before performing the lung function tests. Long-acting bronchodilators were withheld at least 12 hours before the test, and short-acting bronchodilators 4 hours before the test. Participants who tested positive for COVID-19 were excluded from the study and were referred to the nearest healthcare clinic for further assessment.

Participants with negative results were allowed to continue in the study. They were asked to perform pre- and post-bronchodilator IOS and spirometry.

IOS was conducted first, followed by spirometry to avoid the influence of forced expiration on IOS parameters. Following that, participants were given bronchodilator via nebulisation with 400mcg Salbutamol, and both spirometry and IOS tests were repeated. Positive bronchodilator response (BDR) was 12% and greater than 200ml increased in FEV_1.[6]

IOS (Carefusion Germany 23X) was performed following a standardiszed protocol based on the manufacturer's instructions. Participants sat in a neutral position with a nose clip in place. An impulse generated by the loudspeaker was connected to the subject's mouth. The frequency ranges from 5 to -30 Hz were delivered. Resistance at 5Hz (R_5) and 20 Hz (R_{20}) were measured.

Spirometry was performed using SpiroUSB (CareFusion Germany 23X). Participants were asked to blow out for at least 6 seconds according to the American Thoracic Society (ATS) criteria.[6] This was performed at least three[3] times and a maximum of 8 tests depending on the quality of the test. A minimum of three[3] acceptable measurements were recorded for each participants, and the test was only be considered if fulfilled acceptability and repeatability criteria for FEV_1 and FVC.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) software version 26 was used for data analysis. Variables were expressed as mean ± SD. Independent -t test, one-way ANOVA, Kruskal–-Wallis test, and Pearson correlations were used for comparisons. Correlation coefficient (r) was used to examine the relationship between measures. A P- value of ˂ 0.05 was considered statistically significant. Numerical analysis was used for the ROC curve, including the AUC, sensitivity, specificity, and optimal cut-off values for the IOS parameter.

RESULTS

A total of 82 participants were recruited. The mean age of all participants was 45.8 years + 15.0 years. Majority 48 (58.5%) were females, and 34 (41.5%) were males. Majority of the participants, 68 (82.9%) had good asthma control (ACT score > 20) and 14 (17.1%) had poorly controlled asthma (ACT score < 19). Table I describes the demographics of the study population.

Participants were further divided into four groups based on the BDR and airflow obstruction ($FEV_1/FVC < 0.7$). The four groups were obstructive +/- BDR and non-obstructive +/- BDR. 28 participants were categorised in the obstructive group, of which 19 were BDR positive, and 9 were BDR negative. 54 participants were classified under the non-obstructive group which 17 of them were BDR positive and 37 BDR negative.

A one-way between-group analysis of variance (ANOVA) was used to investigate the association of demographic characteristics with the bronchodilator response (BDR) group for normally distributed data. Inspection of skewness, kurtosis and Shapiro–Wilk statistics indicated that the assumption of normality was supported (Age, FEV, FEV_1, FEF and FVC) in each of the conditions. Levene's statistics were not significant for Age, FEV, FEV_1, FEF and FVC, R_5, R_{20}, X_5 and AX.

Post-hoc analyses with Tukey's Honest Significant Difference (HSD) test (using an α of .05) for age revealed the group of obstructive, BDR negative (M = 60.00, SD + 13.49) has significantly higher age compared to the non-obstructive, BDR negative group (M = 42.51, SD + 14.09).

Post-hoc analyses with Tukey's HSD (using an α of .05) revealed that obstructive group, BDR positive had lower pre-bronchodilator FEV_1 (L) (M=1.71, SD+0.51), and FEV_1, % predicted (M= 59.95%, SD+15.00) compared to non-obstructive, BDR negative group with pre-bronchodilator FEV_1(L) (M=2.21, SD+0.63) and FEV_1, % predicted (M = 81.19, SD + 14.78)

Post-hoc analyses with Tukey's HSD (using an α of .05) for $FEF_{25\%–75\%}$ revealed the group of obstructive, BDR positive (M=31.79, SD + 16.06) has significantly lower values compared to non-obstructive, BDR negative group (M = 70.92, SD + 21.91)

The between-group analysis of participants in BDR positive and negative without airflow limitation is presented in Table II.

An independent-samples t-test was used to compare two groups: positive (n=36) and negative (n=46), with a bronchodilator reversibility test.

For FEV_1 (L), the t-test was statistically significant, in which BDR negative group (M = 2.12, SD + 0.72) reporting 0.32L higher FEV_1 (L) value, compared to BDR positive group (M = 1.80, SD + 0.57), t (80) = 2.185 p = 0.032, two-tailed.

For FEV_1,(% predicted) the t-test was statistically significant, in which BDR negative group (M = 78.46, SD + 17.94) reported a 12.24% higher FEV_1 value compared to BDR

Table I: Participants' demographic, ACT score, spirometry and IOS characteristics between obstructive and non-obstructive group

Parameter	Obstructive group FEV1/FVC <0.7		Non-obstructive group FEV1/FVC >0.7		p-value
	BDR positive	BDR negative	BDR positive	BDR negative	
Characteristics					
N	19	9	17	37	
Age	44.7 +14.66	60.00 + 13.49	46.6 + 14.77	42.5 + 14.09	0.016
Male, n (%)	12 (63.2)	6 (66.7)	6 (35.3)	10 (27)	0.022
Female, n (%)	7 (36.8)	3 (33.3)	11 (64.7)	27 (73)	0.022
ACT score	22.16 + 3.01	23.33 + 1.23	21.94 + 2.90	22.00 + 2.94	0.622
Spirometry					
FEV_1 (L)	1.7 + 0.6	1.7 + 0.9	1.9 + 0.5	2.2 + 0.6	0.024
FEV_1 (% predicted)	60 + 15.0	67.2 + 25.5	72.5 + 12.2	81.2 + 14.8	<0.01
FVC (L)	2.8 + 1.0	2.8 + 1.1	2.5 + 0.8	2.7 + 0.8	0.571
FVC (% predicted)	76.5+16.1	80.2+21.9	72.7+ 13.4	77.8+ 3.3	0.075
FEV_1/FVC	0.6 + 0.1	0.6 + 0.1	0.8 + 0.1	0.8 + 0.1	<0.01
$FEF_{25\%–75\%}$,% predicted	31.8 + 16.1	32.8 + 16.5	57.9 + 19.2	70.9 + 21.9	<0.01
$FEF_{25\%–75\%}$<65% predicted n(%)	18 (94.7)	9 (100)	14 (82.4)	18 (48.6)	<0.01
IOS					
R_5 (cmH_20/L/s)	6.4 + 2.0	6.3 + 2.9	5.9 + 2.4	5.5 + 2.3	0.464
R_{20} (cmH_20/L/s)	3.60 + 0.8	3.4 + 0.8	3.5 + 0.9	3.3 + 1.0	0.564
R_{5-R20} (cmH_20/L/s)	2.9 + 1.4	2.9 + 2.3	2.4 + 1.7	2.2 + 1.5	0.46
X_5 (cmH_20/L/s)	–3.2 + 1.7	–2.6 + 1.9	–2.1 + 1.5	–2.2 + 1.3	0.071
AX (cmH_20/L)	25.9 + 15.5	25.9 + 21.6	20.3 + 16.70	17.3 + 13.5	0.2

The data are described using mean + SD or n (%). p-value is for one-way ANOVA for four groups.

Table II: Analysis between the group of BDR positive and negative in total population

Parameter	BDR positive	BDR negative	p-value
Characteristics			
N	36	46	
Age, mean + SD	45.6 + 14.5	45.9 + 15.5	0.92
Male, n (%)	18 (50.0)	16 (34.8)	0.169
Female, n (%)	18 (50.0)	30 (65.2)	0.169
Spirometry			
FEV_1 (L)	1.80 + 0.6	2.1 + 0.	0.032
FEV_1, % predicted	65.9 + 15.0	78.5 + 17.9	0.001
FVC (L)	2.7 + 0.9	2.8 + 0.8	0.595
FEV_1/FVC	0.7 + 0.1	0.8 + 0.1	0.006
$FEF_{25\%–75\%}$, % predicted	44.1 + 21.8	63.5 + 25.8	0.001
$FEF_{25\%–75\%}$ < 65% predicted, n (%)	32 (88.9)	27 (58.7)	0.002
IOS			
R_5 (cmH_20/L/s))	6.2 + 2.2	5.6 + 2.4	0.279
R_{20} (cmH_20/L/s))	3.6 + 0.8	3.30 + 0.9	0.195
R_5–R_{20} (cmH_20/L/s))	2.6 + 1.5	2.33+ 1.7	0.391
X_5 (cmH_20/L/s))	–2.7 + 1.7	-2.3 + 1.4	0.213
AX (cmH_20/L)	23.2 + 16.1	19.0 + 15.5	0.234

The data are described using mean + SD or n (%).

Table III: Correlation of change of FEV_1 and $FEF_{25\%–75\%}$ <65% predicted to IOS parameters

Change of FEV_1	r	p-value
IOS parameters		
Change of R_5	–0.25[a]	0.023
Change of R_{20}	–0.18	0.11
Change of AX	–0.104	0.351
$FEF_{25\%–75\%}$ <65% predicted	R	p-value
IOS parameters		
R_5–R_{20}	–0.34[a]	0.008
X_5	0.46[a]	<0.001
AX	–0.41[a]	0.001

[a]Correlation is significant at the level 0.05 level (two-tailed)
Based on Cohen,1988 classification strength

Table IV: Incidence of SAD defined by $FEF_{25\%–75\%}$ and IOS parameters

Small airway parameters	BDR positive	BDR negative
$FEF_{25\%–75\%}$ < 65% predicted, n(%);	32 (88.9)	27 (58.7)
R_5-R_{20} > 0.07, n(%)	35 (97.2)	42 (91.3)
X_5 < –0.10, n(%)	30 (83.3)	38 (82.6)
AX > 0.38, n(%)	35 (97.2)	42 (91.3)

[a]Pre-bronchodilator values (FEF 25-75)

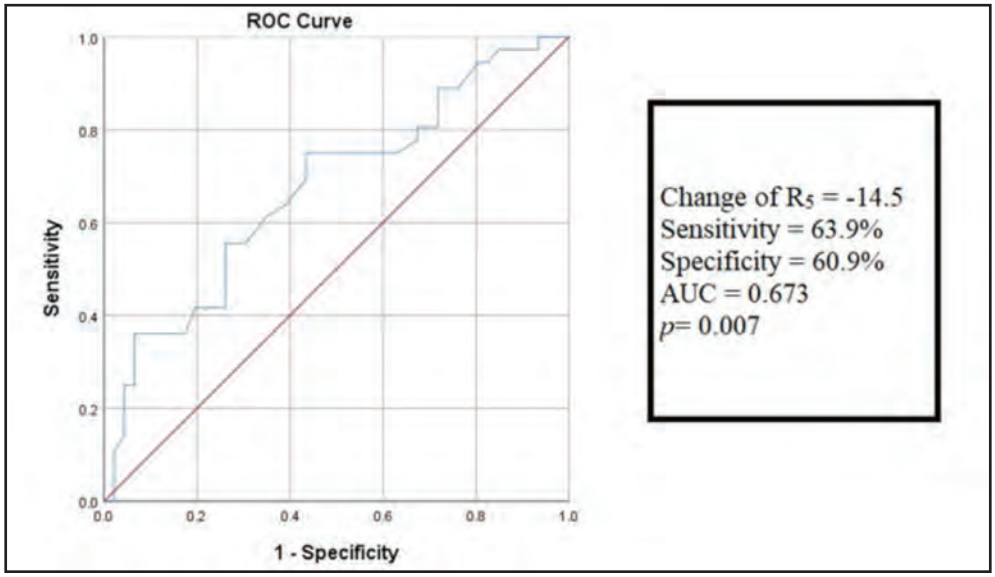

Fig. 1: Receiver operating characteristic (ROC) curve showing the accuracy of spirometry and IOS.

positive group (M = 65.86, SD + 14.98), t (79.1) = 3.304, p = 0.001, two-tailed.

For FEV_1/FVC ratio, the t-test was statistically significant, in which BDR negative group (M = 0.76, SD + 0.12) reported 0.07 higher ratio FEV_1/FVC value compared to BDR positive group (M = 0.69, SD + 0.12), t (80) =2.841, p=0.006, two-tailed.

For FEF 25%–75% the t-test was statistically significant, in which BDR negative group (M = 63.46, SD + 25.82) reported 19.35% higher FEF 25%–75% value compared to BDR positive group (M = 44.11, SD + 21.81), t (80) = 4.055, p < 0.001, two-tailed.

Table III described the correlation between IOS and spirometric parameters of the study population with $FEF_{25\%–75\%}$ <65% predicted. Change of $FEF_{25\%–75\%}$ was correlated with the R_5-R_{20}, X_5 and AX from IOS (Table IV).

Table IV describes the incidence of SAD between BDR positive and negative group. Detection of SAD in BDR positive using IOS was 97.2% compared to spirometry was 88.9%. Especially in the BDR negative group, detection of SAD by IOS was as high as 91.3% compared to spirometry, accounting for 58.7% only (Table IV).

Our study showed that the decrement of 14.5% in R5 can be correlated with positive BDR with the sensitivity of 63.9% and specificity of 60.9% (Figure 1).

DISCUSSION

Our study showed a correlation between IOS with bronchodilator reversibility in asthmatic participants. We found a correlation between the change of FEV_1 and the change of R_5. Although the correlation was weak, it was statistically significant. The weak correlation between IOS and spirometry parameters could be due to sample size limitation and the fact that spirometry is an effort-dependent procedure while IOS is relatively easier to perform. The other parameters from the IOS (e.g., change of R_{20} and change of AX) did not show any significant correlation to the change of FEV_1 from the spirometry.

There is no direct comparison study to compare cost-effectiveness of using spirometry and IOS in diagnosing asthma. However, in general, spirometry is generally considered more cost-effective due to its widespread use, established protocols and lower equipment costs. The training required for technicians and healthcare professionals is widely available and less specialised. Spirometers are relatively affordable and have become a standard diagnostic tool.

On the other hand, IOS tends to be more expensive, both in terms of equipment and training. The devices used in IOS are more sophisticated and can incur higher initial costs. Additionally, specialised training is often required for accurate interpretation, adding to the overall expenses.

While spirometry remains a cost-effective and widely accepted method, the growing recognition of IOS's unique capabilities may impact its cost-effectiveness in the future as technology advances and becomes more commonplace.

Several studies reported that positive BDR as expressed by IOS could be ranged from 8.6% to more than 40%, depending on the population or differentiating the participants' asthma control.[5] However, most of the data showed that a positive BDR was strongly suggested when there was a 40% decrease in R_5.[17] It signified significant airway reversibility in children and adults; however, this cut-off value may not be applicable in differentiating participants with asthma from those without asthma.

The advantage of using IOS is that it requires less effort from the participants. Our study showed that the readings produced from the IOS were able to achieve a satisfactory result compared to the spirometry. It should be considered a preferred tool for detecting BDR, especially for participants with physical and cognitive limitations participants. Even though several studies have proved that parameters from IOS were correlated with spirometry, clinical implications of using the IOS index in adult participants remain under discussion and observation until now.

Apart from the good markers for the diagnosis of bronchial asthma by the IOS indices, it can be used to evaluate disease control, especially in elderly participants.[16] In our study, we could not perform the comparison between different asthma control groups due to sample size limitations.

Our study proved a correlation between $FEF_{25\%–75\%}$ from spirometry to IOS parameters, including R_5-R_{20}, area of reactant (AX) and X_5. From the ECLIPSE trial, the predictive value of SAD was defined as R_5-R_{20} greater than 0.07 kPa/L/s, Ax more than 0.38 kPa/L/s and X_5 lesser than –0.10 kPa/L/s respectively.[18] Our IOS parameters were measured in $cmH_20/L/s$. During the data analysis, we converted the measurement to the unit, kPa/L/s, with the standard value of $1cmH_20$ equal to 0.098 kPa. Our study showed that IOS parameters could detect SAD better than spirometry. Especially in the BDR negative group, detection of SAD by IOS was as high as 91.3% compared to spirometry, accounting for 58.7% only.

Earlier detection of SAD by using spirometry or IOS is essential. The presence of SAD is associated with increased disease severity, risk of frequent exacerbation of asthma attacks and poorer symptom control. It is generally accepted that $FEF_{25\%–75\%}$ in the spirometry with a value of less than 65% predicted the SAD. We need to consider that usage of $FEF_{25\%–75\%}$ is limited when not adjusted by lung volume. While performing spirometry, lung volume is largely influenced by inadequate effort, especially in the elderly and children.

The limitation of the study was the small sample size. Due to the COVID-19 pandemic in Malaysia since March 2020, clinic appointments have been delayed. We also found fewer asthma participants attending the outpatient clinic for fear of contracting COVID-19 infection. To perform the spirometry and IOS, the participants were required to perform the COVID-19 PCR at least 48 hours before the procedure. Unfortunately, although they initially agreed to the study, some participants were not keen/did not turn up for the scheduled COVID-19 PCR test.

In conclusion, our study showed promising results in the correlation of spirometry and IOS. There was a correlation between IOS with bronchodilator reversibility. However, we need to consider the use of bronchodilator may alter the results. Additionally, our study showed a correlation of $FEF_{25\%–75\%}$ and differences between R20 and R5 (R_5–R_{20}) in SAD. The detection of SAD in the asthmatic patient by using IOS was better than $FEF_{25\%–75\%}$, especially in the BDR negative group. IOS can be be considered as an alternative tool to spirometry for the diagnosis of asthma in adults.

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ORIGINAL ARTICLE

Women's empowerment based on self-regulated learning as mother's ability to fulfill nutrition in stunted children

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ABSTRACT

Introduction: The role of providing nutrition to children aged 6–24 months who are stunted is related to the mother's ability to provide proper nutrition. Empowerment of mothers based on self-regulated learning is a nursing intervention that can be carried out by using the abilities, belief and individual capacities of mothers in completing tasks, managing and providing nutrition to children aged 6–24 months. Mother's characteristic are motivation, self-esteem, self-efficacy, knowledge, belief and ability to decision-making about providing nutrition to children, so it can be a learning process for the mother in using resources which improve the nutrition ability of the mother. This study aims to apply a women's empowerment model based on self-regulated learning in increasing the mother's ability to fulfill nutrition in stunted children aged 6–24 months.

Materials and Methods: The research design used a quasi-experiment. The sampling technique used cluster sampling with 76 respondents in intervention group and 76 respondents in control group. The research was conducted in the working area in Public Health Center, Malang Regency. Data analysis in this study used the Wilcoxon Signed Rank Test and Mann–Whitney.

Results: The results of the study found that there were differences in the ability of mothers to fulfill nutrition in stunted children between the intervention group and the control group (p = 0.000). There were mean differences in the ability of mothers to fulfill nutrition for stunted children before and after the intervention in the intervention group with indicators of breastfeeding, food preparation and processing, complementary- feeding and responsive feeding were increased (p = 0.000). However, in the control group, there were no differences in the ability of mothers to fulfill nutrition with indicator breastfeeding (p = 0.462), food preparation and processing (p = 0.721), complementary feeding (p = 0.721), complementary feeding (p = 0.462). (p = 0.054), responsive feeding (p = 0.465) and adherence to stunting therapy (p = 0.722).

Conclusion: The women's empowerment model based on self-regulated learning is formed by individual mother factors, family factors, health service system factors, and child factors so that it can increase the mother's ability to fulfill nutrition in children aged 6–24 months who are stunted. The women's empowerment is a learning process about breastfeeding, food hygiene, infant and young children feeding, and responsive feeding by mothers to fulfill nutrition in children with stunting, with a goal and plan to achieve an improvement in mother's ability and nutritional status in children.

KEYWORDS:
stunting; women empowerment; ability; nutrition

INTRODUCTION

The role of feeding in the first 2 years of life is closely related to the mother's ability to fulfill nutrition, because at this age children are at risk of experiencing nutritional problems due to transition or weaning and feeding practices of infants, especially in terms of food variety, quality of diet, availability and accessibility, nutritious food, exposure to infection and poor sanitation.[1] In addition, mothers provide food to children based on the child's expressed hunger response, the food menu is prepared based on the wishes of the child and the large use of instant solids is considered more practical.[2] The quality of food and nutrition depends on the mother's ability to feed children aged 6–24 months.[3] Mothers who have a good knowledge influence parenting patterns including feeding, food consumption patterns and nutritional status.[4]

Mothers are part of the family members who have autonomy and a nurturing role in feeding infants and children and are able to make decisions, especially regarding the health of children.[5] Mother's knowledge and skills are needed as a basis for fulfilling child nutrition, mothers must be able to apply parenting in terms of feeding children (responsive feeding) which includes providing food according to the child's age, sensitivity of the mother regarding child's mealtime, creating a good and comfortable.[5] Infant and Young Children Feeding (IYCF) requires a variety of food variations, portions increased gradually, food consistency, and a balanced proportion of macro-micronutrient, including vegetables, fruits, side dishes (sources of animal and vegetable protein) and staple food as energy sources.[6]

Self-regulated learning is a method that can be used by mothers by using their abilities, beliefs and capacities so that mothers' self-regulation, abilities and self-control are more directed.[7] Individual capacities are part of the self-regulated element in which the mother's beliefs and abilities in

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completing tasks, organising and acting on feeding infants and children aged 6–24 months who are stunted are employed to achieve their role in feeding practices so that children's nutrition can be fulfilled.[8]

Efforts and strategies that can be carried out in dealing with the problem of stunting are specific nutritional interventions targeting breastfeeding mothers and children under 23 months of age. Specific interventions that can be carried out are encouraging early initiation of breastfeeding; encouraging exclusive breastfeeding; promotion and education of appropriate complementary foods; tackling worm infections in mothers and children; providing zinc supplementation to children; iron fortification into food/supplementation of micronutrients; prevention and clinical management; administration of complete immunisation; prevention and treatment of diarrhoea; implementation of the principles of management of sick toddlers; supplementation of vitamin A in children 6–59 months; management of severe acute malnutrition in children; and monitoring of child growth and development.[9] In addition, nutritional-specific interventions that can be carried out in stunted and moderately malnourished children are increasing IYCF and improving diet in infants and toddlers with strategies to increase the variety of foods, especially those containing animal protein and fortified milk, giving multiple micronutrients (zinc, iron, vitamins A).[10]

Women's empowerment is influenced by family and environmental factors as well as the resources they have. Support from family, groups and mother's involvement in social activities (e.g., integrated health service) can influence mother's attitude and behaviour. Social participation here is a potential behaviour to transform individuals so they can adapt to the environment.[7] This requires the role of empowering mothers with a self-regulated learning approach in an effort to improve family health, especially for toddlers, so that efforts to improve nutrition for toddlers can be overcome. Empowering mothers with a self-regulated learning approach is carried out by maximising the resources owned by mothers and families where mothers who learn actively as regulators of their own learning process start from planning, monitoring, controlling and evaluating themselves systematically to achieve learning goals, using both cognitive, motivational and behavioral.[5] Good knowledge, positive attitude, mother's autonomy and support from the environment will influence mother's self-esteem and self-efficacy on her ability to fulfill nutrition in children. This is a component that can predict the mother's ability to choose to start providing adequate nutrition.[11] One model that will be developed as a nutritional intervention for stunted children is self-regulated learning by maximising the resources owned by mothers in the family so that mothers are able to carry out self-regulation, especially in carrying out roles in terms of parenting and fulfilling nutrition in children starting from infant and child feeding practices so that problems related to nutrition in children aged 6–24 months who experience stunting can be resolved.[12]

MATERIALS AND METHODS

The research study used a quasi-experimental. The research design was used to compare the effectiveness of the intervention given to the intervention group with the control group before and after the intervention. In conducting the research, the intervention group received standard care from public health centre and was given women's empowerment interventions (used module), while the control group only received standard care from public health centre. The module as a media for women empowerment based on Self- regulated learning SRL) was given in 12 weeks (8 weeks of mentoring, coaching and 4 weeks of independent learning). Every week, mother has done to finished knowledge and ability to improve women empowerment about infant and young children feeding.

This study was conducted among mothers who have stunted children aged 6–24 months in Public Health Center Malang Regency, East Java, Indonesia. Population in this research are mothers who have stunted children aged 6–24 months. Sample in this study was divided into two groups: intervention and control group using cluster sampling on January–April 2023. Sampling technique in this research used randomised (cluster sampling) to recruit the participants with criteria: Inclusion criteria: Mothers aged 20–45 years; mothers who have children two or more, breastfeed their children, cooperative with in complying with agreed activity rules. Exclusion criteria: Mothers was not live at home with children and not prepare food for children, mothers who had only child.

The independent variable in this study was women's empowerment based on self-regulated learning while the dependent variable was the mother's ability to fulfill nutrition in children aged 6–24 months who are stunted.

Retrieval of research data used a questionnaire taken from the modification of infant and young children feeding where the instrument has been tested for validity and reliability. Validity of this research instrument obtained a value of r = 0.367 and the reliability results showed that the Cronbach's alpha result was 0.916 (reliable).

Descriptive analysis for categorical data used the frequency distribution, and for numerical data used the mean, standard deviation (SD), minimum (min) and maximum (max) values. Data were analysed using Wilcoxon Signed Rank Test and Mann Whitney.

Ethical Considerations

Respondents were given informed consent by signing a consent letter as research subjects for interviews and filling out questionnaires, discussions, and observations. Researchers delivered informed consent and explained the research objectives, voluntarism and the ability to understand the information. This study was approved by the Health Research Ethics Committee, Faculty of Nursing, Universitas Airlangga Surabaya no 2574-KEPK in 2022

RESULTS

The research was carried out in the Public Health Center, Malang Regency, East Java, Indonesiawhere this location has 12 villages with a total of 166 children under 5 experiencing stunting out of 5158 children under 5 (3.2%). This research was conducted in two villages with the highest number of

Table I: Test for equality respondent characteristic between intervention group and control group in mother with stunted children (n = 152)

Variable	Group		p- value
	Intervention (n = 76)	Control (n = 76)	
Age of Mother			
17–25 years old	18 (23.7%)	12 (15.8%)	0.440[a]
26–35 years old	36 (47.36%)	32 (42.10%)	
36–45 years old	22 (28.94%)	32 (42.10%)	
Pendidikan			
Elementary school	4 (5.26%)	8 (10.52%)	0,483[a]
Junior high school	16 (21.05%)	8 (10.52%)	
Senior high school	38 (50%)	36 (47.36%)	
Higher education	18 (23.69%)	24 (31.6%)	
Occupation			
Farmer	2 (2.63%)	0	0.569[a]
Enterpreunership	18 (23.69%)	16 (21.05%)	
Housewife	56 (73.68%)	60 (78.95%)	
Age of children			
6–12 month	8 (10.52%)	8 (10.52%)	0.644[a]
12–24 month	68 (89.48%)	68 (89.48%)	
Method of child birth			
Spontan	58 (76.31%)	48 (63.15%)	0.212[a]
Sectio secarea	18 (23.69%)	28 (36.84%)	

[a]Chi square test.

Table II: Differences in mother's ability to fulfill nutrition in children aged 6–24 month

Variable	Intervention group			Control group			Different test		
	Pre Mean ± SD	Post Mean ± SD	p-value	Pre Mean ± SD	Post Mean ± SD	p-value	Pre–pre	Post–post	Δ
Breastfeeding	63.84 ± 9.96	74.63 ± 6.85	0.000	62.63 ± 10.5	64.21 ± 7.83	0.462	0.428	0.000	0.000
Food preparation and processing	64.63 ± 9.76	95.10 ± 5.35	0.000	63.10 ± 9.21	63.84 ± 8.66	0.721	0.450	0.000	0.000
Complementary feeding	71.81 ± 6.22	87.31 ± 6.89	0.000	63.86 ± 8.51	67.52 ± 7.77	0.054	0.000	0.000	0.000
Responsive feeding	66.13 ± 7.63	87.92 ± 7.27	0.000	63.39 ± 8.78	64.84 ± 8.39	0.465	0.196	0.000	0.000
Adherence to stunting therapy	84.97 ± 7.34	96.26 ± 5.63	0.000	81.97 ± 8.61	82.68 ± 8.74	0.722	0.361	0.000	0.000

children aged 6–24 months who were stunted, Petungsewu (16.5%) and Sumbersuko (12.4%) areas.

The following are the results of the test for equality of the characteristics of the respondents' demographic data between the intervention group and the control group before being given the intervention. Assessment of the description of the characteristics of the respondents based on the results of the descriptive analysis is presented in the form of a frequency distribution table in the form of percentage and frequency values, mean values and standard deviations.

Table I shows that the highest proportion of ages in the intervention group is at the age of 26–35 years (47.36%), while the control group has the highest proportion at the ages of 26–35 years and 36–45 years (42.10%). The highest proportion of mothers with high school education (50%) in the intervention group and control group. The highest proportion of mother's work was housewife (73.68%) in the intervention group and control group (78.9%). The proportion of children aged 12–24 months in each intervention group and control group (89.48%).

Mother's ability to fulfill nutrition in children aged 6–24 months who experience stunting before and after the intervention of the women's empowerment model is based on self-regulated learning where the results of measuring the ability of the mother are carried out one month after the intervention is carried out. The following are the results of measuring the ability of mothers carried out before and after the intervention.

Based on Table II, it shows that the average score of mothers' ability to fulfill nutrition in children aged 6–24 months who experience stunting has increased between before and after the intervention in both the intervention group and the control group. From the results of statistical tests using the Wilcoxon Signed Rank Test, it was found that there were differences in the ability of mothers to fulfill nutrition in children aged 6–24 months who were stunted before and after being given interventions with indicators of breastfeeding (p = 0.000), food preparation and processing (p = 0.000), complementary feeding (p = 0.000), responsive feeding (p = 0.000) and adherence to stunting therapy (p = 0.000). Whereas in the control group, there was no difference between the abilities of mothers in children aged 6–24 months who were stunted before and after being given standard interventions with indicators of breastfeeding (p = 0.462), food preparation and processing (p = 0.721), complementary feeding (p = 0.721), complementary feeding

(p = 0.462). p = 0.054), responsive feeding (p = 0.465) and adherence to stunting therapy (p = 0.722).

In addition, other variables contained in this study from the results of the Mann–Whitney test found that there was a significant difference between the mother's ability to fulfill nutrition between the intervention group and the control group, which included breastfeeding practices (p = 0.000), food preparation and processing (p = 0.000), complementary feeding (p = 0.000), responsive feeding (p = 0.000) and adherence to stunting therapy (p = 0.000).

DISCUSSION

Women are empowered to be leaders in the nutrition approach. The nutrition-specific intervention will contribute more to the reduction of malnutrition and lead to a sharper decline in the proportion of stunted children, which can improve the nutrition status directly. In practice, mothers provide food to children based on the hunger response expressed by the child; besides that, the food menu is prepared based on the child's wishes, and the use of instant complementary foods is considered more practical. Mothers are part of the family with autonomy and a nurturing role in feeding infants and children and can make decisions, especially regarding children's health. Mothers' knowledge and skills are very necessary as a basis for fulfilling child nutrition. Mothers must be able to apply parenting in terms of providing food to children (responsive feeding), which includes feeding according to the child's age, the mother's sensitivity regarding the child's eating time, and creating a good and comfortable child's eating atmosphere. Complementary feeding in infant and child requires a variety of food variations, gradually increasing portions, food consistency and balanced proportions of macro-micronutrients, including vegetables, fruits, side dishes (sources of animal and vegetable protein) and staple foods, such as a source of energy.

Maternal autonomy in decision-making is a factor related to maternal empowerment, especially concerning child health. The mother's ability to make decisions becomes a strength in maintaining health and providing household needs so that the nutritional needs of families, especially children, can be met properly. Empowering women or practical mothers with stunted children positively impacts into the children. Previous studies found that women's empowerment in the household is generally associated with children's nutritional well-being and focuses on mothers who have a role to fulfill in the nutritional status of stunted children.[13] Contribution of mother's ability is to access information, mobility, ability of decision-making about child-care, and child health.[14,15] A mother with children under six years, especially infants and toddlers, can screen for the risk of stunting. It is essential so that several ways can be adopted to prevent it. The examples are by providing adequate quantity and quality of food and maintaining the health of toddlers from infectious diseases, especially tracking gastrointestinal infection so that toddlers can achieve a catch-up growth. Then, planning public strategies can help to control childhood undernutrition according to underlying factors. Health promotion about nutritional adequacy, especially responsive feeding, supplementary feeding, or practical feeding from mother to child, may improve children's nutritional status.

Another factor based on family, was influenced by type of family, stress, coping, role and family social support. Families with social functions, barriers, functions, coping, stress, roles, and types in caring for children experiencing stunting have an important effect on empowerment. This is in line with Friedman's (2010) theory that social, economic, environmental, family type, and cultural factors will affect the nursing process. Previous research has shown that family factors can influence children's growth, including family income, parental education, employment status, access to healthcare, and parental health behaviour. Indonesia, especially in Java, still adheres to a patriarchal culture, which places women as people who play a role in child-care, including children's health problems. This encourages women to take care of the household by managing the resources owned by the family, which is the main key to the nutritional status of children. The environment, in this case, the family, is the driving factor in reducing the incidence of stunting. It is because women are empowered independently and can maximise crop livestock production, aiming to meet the nutritional needs of children in the household to reduce the incidence of stunting. Empowerment of mothers can increase the knowledge of mothers and families because stunting is caused by several factors, including maintaining cleanliness by washing hands, which can be done as an effort to prevent stunting.[16,17]

The health service system factor is influenced by health information sources, the role of nurses, the role of cadres, the affordability of access to health service sources where the research results. Promotive and preventive programs in efforts to prevent stunting require an important role from an integrated and sustainable healthcare system. This is because the impact arising from stunting will affect children's development. Health services affect health by prompt handling of health problems, especially nutritional problems. Services that are always ready and close to the community will greatly assist in improving health status.

Child factors are influenced by body weight, history of infection, difficulty eating in children and eating patterns in children. Where, from these factors, body length does not affect maternal empowerment. This is because stunting does not directly affect birth length. The study conducted shows that self-regulated learning-based women's empowerment can influence the ability of mothers to optimally feed infants and children with indicators of breastfeeding, food preparation and processing, infant and child feeding, responsive feeding, and adherence to stunting therapy in children. Infants and children aged 6–24 months need proper food intake to achieve optimal growth and development, especially during the first 1000 days of life. Unmet nutritional needs result in babies experiencing malnutrition, stunting, wasting, not optimal brain intelligence, decreased immune system and problems with stunted growth and development, even death. In infants aged 0–6 months, nutritional needs are met through exclusive breastfeeding. The content of carbohydrates, proteins, fats, vitamins, minerals, cholesterol, vitamin D and fluorine contained in breast milk makes

babies aged 0–6 months get a balanced nutritional intake. Entering the age of 6 months, babies are already getting complementary foods to fulfill their nutritional intake. Digestion is ready to consume complementary foods, so that children can start to be given complementary foods such as biscuits or milk.

After the baby is more than 6 months old, the need for food intake is not only sufficient through breast milk. Complementary food for ASI needs to be given to babies in stages according to the type, quantity and texture according to the baby's age; meanwhile, breastfeeding for children does not need to be stopped until the child is 2 years old. Complementary foods for children can be given to children according to the age of the child where at the age of 6–9 months the child can be given soft or mashed food, at the age of 9–12 months they can be given soft textured foods such as filtered porridge or steamed rice, and at the age of 12–24 months old can be given food with a solid texture where previously it can be started with coarsely chopped food and gradually adjusted to the child's ability until the food menu can be adapted to the family menu.

In introducing breastfeeding to children, within the first 2 weeks it is recommended to introduce porridge and a single fruit with a frequency of 1–2 meals a day. This introduction period is used to introduce variations of carbohydrate sources, vegetable and fruit. In the following week, the child should be introduced to protein, both animal and vegetable protein, and additional sources of fat in the form of refined/filtered porridge given along with carbohydrates and vegetables with a frequency of meals 2–3 times a day and begin to be introduced to snack foods. The principle of this variety of food is the basis for compiling a daily menu so that the macro and micronutrient needs of children can still be met. While the parenting pattern in providing food in this case is responsive feeding. Responsive feeding when feeding, is the child's response with a smile, maintaining eye contact, encouraging positive words, and giving children soft food that can be held to stimulate active self-feeding (finger snacks).

Based on the results of research data analysis, the strength of implementing the SRL-based mother empowerment model in this study is that it has high flexibility in learning as an effort to improve mothers' ability to fulfill nutrition in children aged 6–24 months who are stunted, which can be done anywhere and anytime. The development of an SRL-based mother empowerment model is also supported by Bandura's theory of increasing self-efficacy.[18] The integration of the SRL phase into the mothers' empowerment model can increase the ability of mothers in fulfilling nutrition in children aged 6–24 months who are stunted. Thus, the implementation of the model is one of the recommendations for nursing interventions, especially in the community service providers at the forefront who can carry out early detection of growth disorders in children so that they can be carried out effectively and reflect the maximum ability of mothers in feeding infants and children.

The developed women empowerment based on SRL can be an intervention option, especially in child nursing in the community environment to improve mothers' ability to fulfill nutrition in children aged 6–24 months who are stunted.

CONCLUSIONS

The results of the study found that there were differences in the ability of mothers to fulfill nutrition in stunted children between the intervention and control group. The differences in the ability of mothers to fulfill nutrition for stunted children before and after the intervention with indicators breastfeeding, food preparation and processing, complementary-feeding and responsive feeding were increased.

Women's empowerment factors based on self-regulated learning can directly influence mothers' ability to fulfill nutrition in children aged 6–24 months who are stunted. The application of the women's empowerment based on self-regulated learning has proven effective in increasing the ability of mothers to fulfill nutrition in children aged 6–24 months who are stunted. Improving the ability of mothers to fulfill nutrition can be fulfilled by implementing a model of women's empowerment based on self-regulated learning that is adapted to good resources that come from the mother herself, family, health service facilities and children aged 6–24 months who are stunted. Mothers can take advantage of the resources they have, starting from food, family, information about improving health so that by maximising the resources they have in fulfilling nutrition in children, the child's nutritional status can be achieved properly. Other than that, it can be a recommendation where the role of nurses is as counsellor for mothers who have children with nutritional problems and can be used as an intervention recommendation that can be carried out by community nurses.

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ORIGINAL ARTICLE

Patient's satisfaction towards healthcare services and its associated factors at the highest patient loads government primary care clinic in Pahang

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ABSTRACT

Introduction: Patient satisfaction is widely used to monitor the quality of health care services. A significant patient load may influence health care services and patient satisfaction. Klinik Kesihatan Bandar Kuantan, Pahang (KKBK) has the highest patient loads in Pahang state, followed by Klinik Kesihatan Beserah and Klinik Kesihatan Kurnia. There are up to 700 attendees at KKBK per day, representing a population of 209679. KKBK had receives several complaints and patient unhappiness with its health care services, despite the administration's efforts to improve the clinics healthcare delivery. Thus, this study aimed to measure patients' satisfaction towards health care services at Pahang's highest patient loads primary care clinic.

Materials and Methods: A cross-sectional study was conducted at Klinik Kesihatan Bandar Kuantan, Kuantan, Pahang. Patients were selected using stratified random sampling, and 201 participants were selected. The selected participants were asked to fill up the self-administered validated questionnaires consisting of background characteristics and Patient Satisfaction Questionnaire 18 (PSQ-18). Data collection period was from March 2022 to August 2022. Descriptive analysis was used to describe the background characteristics of respondents and the score of patient satisfaction. Multiple linear regression was used to determine the factors associated with patient satisfaction while adjusting for cofounders.

Results: A total of 201 eligible data points were analysed in the study. The respondent mean age was 47.1 ± 16.9. Most respondents were Malay (68.7%), having secondary education (54.2%) and predominantly from the B40 income class (88.1%). The overall mean patient satisfaction score was 3.83 ± 0.31. There were significant associations between overall satisfaction with patient education level (B = −0.144; 95% CI −0.246, −0.042; p = 0.006), waiting time (B = −0.371; 95% CI −0.534, −0.209; p = 0.001) and consultation duration (B = −0.154; 95% CI −0.253, −0.055; p = 0.0020). It was found that patients with secondary education were less satisfied compared to patients with primary education level on health care services they received. Meanwhile, those who were not happy with the waiting time and consultation duration showed less satisfaction with overall healthcare services.

Conclusion: Despite serving the most significant number of patients in Pahang state, most of the patient were satisfied by the health care services at Klinik Kesihatan Bandar Kuantan. However, it is recommended to improve the waiting time and the consultation time in this clinic.

KEYWORDS:
Patient satisfaction; primary care; healthcare services

INTRODUCTION

There has been a growing emphasis on patient engagement in treatment decisions in recent decades. The clinician's job is no longer that of an authoritative figure who 'knows what is best for you.' The clinician and patient interaction has evolved into a collaboration and mutual agreement. Putting the patient at the core of care is a good idea of a healthcare metric.[1] The literature has shown that patient satisfaction has been studied as a dependent, independent and outcome variable to evaluate healthcare services. It also predicts patient health-related behaviours, including adherence to treatment and recommendations of healthcare plans.[2] Patients' perceptions of dissatisfaction contribute to underutilisation or over utilisation at a different levels of healthcare facilities and consequently cause congestion and imbalance of health deliveries.[3]

This study defines patient satisfaction as a subjective assessment of healthcare services provided to patients compared to their expectations.[4] Healthcare authorities have switched to a market-driven strategy, using patient satisfaction surveys to improve organizational performance.[5] For example, a patient satisfaction survey conducted in 50 Massachusetts hospitals led to the adoption of several effective improvement programs.[6] National Health Security (NHS) trusts in England must conduct annual patient satisfaction surveys and report the results of their patient satisfaction to their regulators for further improvement and action on healthcare services given.[7] As a result, measuring patient satisfaction is a legitimate indicator for all healthcare companies or authorities to improve their services and strategic goals.[6] The number of general malpractice litigation verdicts has steadily increased in recent years. In 70% of cases, physicians are acquitted in the malpractice litigation process.[8]

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A patient satisfaction survey could be used to identify doctors who are at a higher risk of patient complaints and malpractice claims;[9] as in Patient Satisfaction Questionnaire 18 (PSQ-18), four out of the seven domains studied concern medical personnel-related factors.[10] The lowest satisfaction score was significantly linked to malpractice activity[8], and interestingly, good patient satisfaction scores bring the healthcare worker a better financial outcome.[11]

The number of patient visits at Klinik Kesihatan Bandar Kuantan (KKBK) was seven times that of the average number of patient visits at other public clinics in Pahang state, which was 111.5 attendees per day,[12,13]. Higher patient loads may result in dissatisfaction with the healthcare services provided. This may be caused by lengthy waiting time and lack of clinician dedication owing to burnout and poor service quality. Patient dissatisfaction will disrupt healthcare delivery systems and reduce treatment adherence.[2] Therefore, this study aims to determine the level of patient satisfaction towards healthcare services provided at Pahang's busiest primary care clinic, with the results could be utilised to identify areas of healthcare that require improvement.

MATERIALS AND METHODS

Study Design and Population

A cross-sectional study was conducted among patients attending Klinik Kesihatan Bandar Kuantan (KKBK), Pahang. The study was conducted over six months, from March 2022 to August 2022. KKBK is a type 3 clinic at Jalan Bukit Sekilau, established in 2013. It covers 209,679 patients; the area of operation is 241 square kilometers. The operational area includes the entire Kuantan City centre, park areas and suburbs, making it the busiest clinic with the highest patient load.

The inclusion criteria were patients 18 years old and above attending KKBK, including first-time (after finished consultation) and follow-up visits. The exclusion criteria were patients with mental health disorder that affect their cognitive function (e.g., schizophrenia and dementia patient), patients attending a maternal and child health clinic as well as those receiving other specialised care (the methadone clinic, the tuberculosis clinic, the emergency ambulance call, domicilliary services). Iliterate patients those who are unable to read or write are not included in the studies.

Stratified random sampling was used in this study. The study population was divided into two strata: the outpatient department and the non-communicable disease department, given only two departments are available in Klinik Kesihatan Bandar Kuantan (KKBK). Each stratum is mutually exclusive, but together they contain the entire population. Stratified random sampling was used to sample from within each stratum.

The single mean formula was used to compute the sample size using the mean from a previous study conducted in primary healthcare which was 68.52 (8.54).[14] The 95% confidence interval with a precision of 1.4 was used. To ensure optimum sample size, a few adjustments were considered as follows:

$$N = \frac{(z\frac{\alpha}{2})2\ \sigma 2}{d2}$$

$N = (1.96)^2 * (8.54)^2 / 1.4^2$
N= 143
Non-response rate = 30% [15]
Non respond calculated by N adjusted = 143 / (1-0.3) = 205; thus, the total estimated sample is 205 respondents.

Study Tools

This study used a questionnaire comprised of two sections. Section A is the sociodemographic data of the respondents. The patient's sociodemographic information, including the respondent's age, gender, race, religion, place of residence, education, income, employment status and marital status, were all gathered through section A. Section B consists of a set of questionnaire to assess patient satisfaction using validated Patient Satisfaction Questionnaire 18 (PSQ-18). This section examines patient satisfaction towards healthcare services utilizing the Marshall and Hays Short-Form Patient Satisfaction Questionnaire (PSQ-18).[10] The questionnaire had been validated among the Malaysian population.[16–18] It is available in English and Malay and consists of 18 questions over seven domains (General satisfaction, technical quality, interpersonal, communication, financial, time spent with the doctor and accessibility and convenience); each rated on a five-point likert scale from one to five (strongly disagree to strongly agree).

The Cronbach's alpha for the questionniare was 0.63–0.79 for the translated questionnaire.[16] Participants were asked to indicate their feelings about the medical care they receive on the Likert scale. According to the PSQ-18 scoring method (Table I), PSQ-18 yields for each of the seven different subscales; general satisfaction (2 items), interpersonal manner (2 items), technical quality (4 items), communication (2 items), financial aspects (2 items), time spent with the doctor (2 items), accessibility and convenience (4 items).

The level of patient satisfaction with each of the seven subscales of healthcare was presented as a score. The sum of all subscales scores may vary from 18 to 90 points, with 18 points being the lowest possible evaluation and 90 points representing the highest possible score[19] and five as the maximum possible mean[20] (Table I). As can be seen in Table I, the score could be presented in three different ways. In the Results section, we presented the score in all three formats for the purpose of comparison with the findings from other studies.

Patients were given a subject information sheet, and those who consented and met the inclusion criteria were recruited into the study. Respondents were identified via stratified random sampling by their queue number system (QMS) at the registration counter. After they understood the patient information sheet and consented, the selected patient was given a unique research ID (subjects will be allowed sufficient time to consider their participation in the study). After consultation with the treating doctor, the patient was directed to a dedicated consultation room with the researcher where a self -administered questionnaire was provided

Table I: Seven domains of patient satisfaction with their calculations and PSQ-18 scoring system

PSQ-18 domain	No. of items	Maximum possible score	Maximum possible mean (Maximum possible score/No. of items)	Level of satisfaction in percentage (Possible score/Maximum Possible score) X 100
General Satisfaction (Items 3+17) (A)	2	10	10/2 items = 5	(A/10) X 100
Technical Quality (Items 2+4+6+14) (B)	4	20	20/4 items = 5	(B/20) X 100
Communication (Items 10+11) (C)	2	10	10/2 items = 5	(C/10) X 100
Interpersonal Manner (Items 1+13) (D)	2	10	10/2 items = 5	(D/10) X 100
Financial Aspects (Items 5+7) (E)	2	10	10/2 items = 5	(E/10) X 100
Time Spent with Doctor (Items 12+15) (F)	2	10	10/2 items = 5	(F/10) X 100
Accessibility and Convenience (Items 8+9+16+18) (G)	4	20	20/4 items = 5	(G/20) X100
Overall satisfaction (Cumulative of all items) (H)	18	90	90/18 items = 5	(H/90) X100

Table II: Background characteristics

Variables		N	%
Age (years)			47.1±16.9*
Gender	Male	121	60.2
	Female	80	39.8
Ethnic	Malay	138	68.7
	Chinese	40	19.9
	Indian	21	10.4
	Others	2	1.0
Religion	Muslim	138	68.7
	Buddha	29	14.4
	Hindu	25	12.4
	Christian	9	4.5
Residential	Urban	175	87.1
	Rural	26	12.9
Marital Status	Married	145	72.1
	Single	47	23.4
	Separated	9	4.5
Education	Primary or lower	43	21.4
	Secondary	109	54.2
	Tertiary	49	24.4
Working Status	Working	120	59.7
	Not Working	62	30.8
	Student	7	3.5
	Pensioner	12	6.0
Income Class			
≥10,960	T20	5	2.5
≥4,850-10,959	M40	19	9.5
< 4,850	B40	177	88.0
Health Insurance	Guarantee letter (GL)	29	14.4
	Non-GL	172	85.6
Self-Perception			
Are you happy with the waiting time?	Yes	160	79.6
	No	41	20.4
Are you happy with the consultation time?	Yes	188	93.5
	No	13	6.5
Department	Outpatient department (OPD)	133	66.2
	Non-communicable disease department (NCD)	68	33.8

*mean ± standard deviation

Data Analysis

The data were analysed using IBM SPSS Statistic version 28.0. Categorical variables were recorded as frequencies and percentages, and numerical variables were recorded as means and standard deviation (SD). The overall patient satisfaction was reported in three components (mean, mean score and percentage) thus the overall patient satisfaction result comparable with others studies. Descriptive analysis was used to describe the background characteristic of respondents and the score of patient satisfaction. The relation between sociodemographic and patient satisfaction was analysed using an independent sample t-test and ANOVA test; both tests were needed as preliminary analysis before we proceeded with multi-linear regression analysis. 95% confidence interval and p-value <0.05 were considered statistically significance. Multiple linear regression was used to determine the factors associated with patient satisfaction while adjusting for cofounders.

Table III: Patient satisfaction level derived from satisfaction items

PSQ-18 Domain	No. of Items	Minimum -Maximum Score	Mean Score ± SD	Minimum -Maximum Mean	Mean ± SD	Satisfaction in Percentage	95% CI
General Satisfaction (Items 3 + 17)	2	4.00-10.00	7.66 ± 1.25	2.72-4.56	3.83 ± 0.31	76.61	74.9,78.4
Technical Quality (Items 2 + 4 + 6 +14)	4	10.00-19.00	15.17 ± 1.72	2.50-4.75	3.79 ± 0.43	75.87	74.7,77.1
Communication (Items 10 + 11)	2	3.00-10.00	7.88 ± 1.13	1.50-5.00	3.94 ± 0.56	78.76	77.2,80.3
Interpersonal Manner (Items 1 + 13)	2	3.00-10.00	7.99 ± 1.17	1.50-5.00	4.00 ± 0.59	79.90	78.3,81.5
Financial Aspects (Items 5 + 7)	2	6.00-10.00	8.05 ± 0.90	3.00-5.00	4.03 ± 0.45	80.55	79.3,81.8
Time Spent with Doctor (Items 12 + 15)	2	3.00-9.00	7.62 ± 1.16	1.50-4.50	3.81 ± 0.58	76.22	74.6,77.5
Accessibility and Convenience (Items 8 + 9 + 16 + 18)	4	8.00-18.00	14.55 ± 1.70	2.00-4.50	3.63 ± 0.42	72.74	71.6,73.9
Overall Satisfaction Score (Cummulative of all items)	18	49.00-82.00	68.93 ± 5.57	2.72-4.56	3.83 ± 0.31	76.59	75.7,77.5

Table IV: Association between background characteristics with mean overall patient satisfaction

Variables		Overall satisfaction (Mean)		
		Mean ± SD	Test	p value
Mean Age (Years)		47.1 ±16.9	0.036****	0.607
Gender	Male	3.85±0.31	1.035*	0.302
	Female	3.80±0.31		
Ethnic	Malay	3.83±0.35	0.659**	0.578
	Chinese	3.81±0.23		
	Indian	3.86±0.25		
	Others	4.11±0.31		
Religion	Muslim	3.82±0.35	0.464**	0.708
	Hindu	3.89±0.15		
	Christian	3.86±0.14		
	Buddha	3.80±0.26		
Residential	Rural	3.70±0.42	1.791*	0.084
	Urban	3.85±0.28		
Marital Status	Single	3.83±0.30	0.802**	0.922
	Married	3.83±0.31		
	Separated	3.79±0.41		
Education Level	Primary or lower	3.93±0.20	3.907**	0.022***
	Secondary	3.78±0.36		
	Tertiary	3.86±0.25		
Working Status	Working	3.84±0.31	1.491**	0.218
	Not working	3.80±0.30		
	Student	3.63±0.40		
	Pensioner	3.91±0.27		
Income Class (RM)				
≥10,960	T20	3.64±0.33	2.592**	0.077
≥4,850-10,959	M40	3.95±0.31		
< 4,850	B40	3.82±0.33		
Health insurance	Guarantee letter (GL)	3.82±0.30	0.138*	0.891
	Non-GL	3.83±0.31		
Are you happy with the waiting time?	Yes	3.86±0.31	2.975*	0.003***
	No	3.70±0.29		
Are you happy with the consultation time?	Yes	3.85±0.28	3.253*	0.006 ***
	No	3.45±0.44		
Department	Outpatient department (OPD)	3.84±0.30	0.398*	0.691
	Non-communicable disease department (NCD)	3.82±0.33		

p<0.05 considered as significant, **F (One-Way Anova), *t (Independent T test) , Pearson correlation*

RESULTS

Background Characteristics

The overall response rate of the study was 98 % (n = 201). Table II shows the background characteristics of the respondents. The respondent's mean age was 47.1 (16.9). Most respondents were male (60.2%), Malay (68.7%) and married (72.1%)—more than half (54.2%) were from secondary education level. The majority came from an income level of B40 (88.1%), with no guaranteed letter (85.6%) and working (59.7%). Most of the patients reported that they were happy with the waiting time (79.6%) and the time spent with the doctor (93.5%) (Table II).

Patient Satisfaction Level Based on PSQ-18 Domain

Based on Table III, the overall satisfaction means found in this study was 3.83 ± 0.31. The highest mean was from the

Table V: Factors associated with mean overall patient satisfaction

Variables	Overall satisfaction (mean) Multiple linear regression[a]			
	Adj.B[b]	95% CI	t-stat	*p* value
Education Level [secondary (reference)]				
Primary or lower	0.144	0.042,0.246	2.787	0.006*
Tertiary	0.051	–0.47, 0.148	1.026	0.306
Are you happy with the consultation time? [yes (reference)/no]	–0.154	–0.253, –0.055	–3.068	0.002*
Are you happy with the waiting time? [yes (reference)/no]	–0.371	–0.534, –0.209	–4.504	0.001*

[a]r2 = 0.172. The model fits reasonably well. Model assumptions are met. There is no multicollinearity problem.
[b] Adjusted regression coefficient, *p < 0.05 considered as significant.

financial aspect (4.03 ± 0.45) with the lowest mean observed in accessibility and convenient (3.63 ± 0.42). Table III shows this study's overall satisfaction mean score was 68.93 ± 5.57. The overall satisfaction percentage found in this study was 76.59%. The highest mean was on the financial aspect (80.55%), with the lowest percentage of satisfaction on healthcare services observed in accessibility and convenient aspect (72.74%).

Association Between Background Characteristic with Mean Overall Patient Satisfaction

A significant association was found between overall satisfaction with education level (p = 0.022), waiting time (p = 0.003) and consultation duration (p = 0.006) (Table IV).

After adjusting for confounder using multiple linear regression analysis, it was found that patients with primary education were more satisfied than those with secondary education levels on the healthcare services they received. Meanwhile, those who were not happy with the waiting and consultation duration showed less satisfaction with overall healthcare services (Table V).

DISCUSSION

Level of Patient Satisfaction

Our study found a positive overall patient satisfaction mean result of 3.83 ± 0.31. The overall satisfaction mean score found in this study was 68.93 ± 5.57, and the overall patient satisfaction with healthcare services in percentage was 76.59 %. We shared almost identical mean scores with the study conducted at University Malaya Medical Centre (UMMC) primary care, which had total patient satisfaction mean score of 67.18 ± 6.67.[18] KKBK and UMMC primary care clinics have high patient loads, are located in busy cities and have much longer appointment intervals.

Meanwhile, another study in International Islamic University Malaysia (IIUM) family health clinic had a lower patient load and thus showed better overall patient satisfaction mean score of 70.75 ± 10.56. The treating physician experience also contributes to patients' satisfaction with healthcare services received.[18] The treating physician at IIUM family health clinic was a registrar and family medicine specialist, which led to better communication and interpersonal skills[17] unlike in KKBK, as most of the treating physicians were medical officers and not in specialist training that may affect patient satisfaction on the healthcare services they received.

Several other local studies reported a proportion of satisfied patients ranging from 78.8% to 93.1%[21–23] and lower satisfied patient rates ranging from 19.4% to 30.7%.[24,25] The difference might be due to different instruments in measuring patient satisfaction. A local study with very high level of patient satisfaction (93.1%) hypothesised that high patient satisfaction was related to the 'generosity factor' of patients who provided high scores on questionnaires. This phenomena contributes to the worry of compromising future treatment if a person's honest personal opinion, which could be interpreted negatively by healthcare service provider.[21]

Our study finding was comparable with our neighbouring countries' primary care, such as Indonesia, with overall satisfaction mean score of 68.52 ± 8.54[14] and better than other parts of the world, such as Lithuania Europe, with their overall satisfaction mean score in primary care clinics of 59.9 ± 14.6.[19] Our study had higher overall patient satisfaction on healthcare services (76.59%) compared to Egypt, 55.9%[26] and a higher overall satisfaction mean of 3.83±0.31 compared to India, 2.97 ± 0.37. Dissatisfaction in the primary care clinic was due to long waiting, healthcare facilities, doctors' behaviour and nonavailability of medicines.[14,27] Different countries had different health policies, the standard of care and advancements in facility and service availability, perhaps making patient satisfaction more complex and variable.

Looking at different settings, the busiest medical outpatient department in a tertiary centre in Hospital Tengku Ampuan Rahimah (HTAR), Klang, it was found that the total mean satisfaction score was much lower, 59.2±6.5 compared to our result of 68.93 ± 5.57. Even in different settings, the findings showed that busy clinics affect patient satisfaction.[16] The finding of our study is in concordance with other studies, which showed that primary care showed better patient satisfaction than tertiary settings.[28] This may be contributed by patient-centredness practice at the primary care level compared to a more disease-focused tertiary centre setting.[17]

Even though the majority (88.1%) of our respondents were from the B40 group and did not have insurance coverage (85.6%), the financial aspect had the highest mean score of overall patient satisfaction level at KKBK, 8.05 ± 0.90. This is most likely due to the Malaysian healthcare system in which the government highly subsidised healthcare systems.[29] Sinuraya et al. reported lower score in the financial aspect, 7.56 ±1.63. The financial aspect became a problem for patients in Indonesia as their national health coverage did

not cover medical examinations, and patients needed to spend money to get medical services.[14] Lower satisfaction on the financial aspect was found in both local studies at UMMC primary care with a mean score of 7.53 ± 1.34, and IIUM family health clinic mean score of 7.86 ± 1.69 as both clinics are paying clinic and only partially subsidised by the Malaysian government and thus, the patient was expecting more on the treatment and outcome.[17,18]

In terms of accessibility and convenience, we had the lowest percentage, 72.74%, among all other domains in PSQ-18. During the time of data collection, most patients felt uneasy as they needed to set an appointment prior to seeing the doctor due to the COVID-19 pandemic, not as before in which they can just walk in to get the health services. High patient loads make the patient wait longer for an appointment. Regardless of the pandemic and high patient load, KKBK still has a better score on accessibility and convenient compare to UMMC primary care, which scores only 66.40%. The possible reason for this finding is that KKBK is located within the community and, therefore, close to the patient's residence and making it easy to reach compared to UMMC primary care locality, which is located at a robust business centre, despite the patient having difficulty of setting for an appointment at KKBK, the patient felt KKBK is easy to reach.

Association Between Background Characteristics with Level of Patient Satisfactions

A significant association was found between overall satisfaction mean with education level (p = 0.022). It was found that patients with primary education were more satisfied compared to patients with secondary education level on healthcare services they received. Our study finding was in concordance with Ganesegaran et al. as it was discovered that overall contentment is highly related to a patient's education level, with patients with higher education reporting lower satisfaction mean scores than those with less education.[16] The patients with a higher level of education were less satisfied since they have higher education, higher income and social status.[30] There was a trend for less educated patients to receive fewer preventive services but had higher time for a physical examination with limited time to attend to patient questions, counselling and negotiation. Less educated patients were less likely to report their expectations during medical visits.[31]

Patient considers patient centeredness (shared decision-making, receiving intelligible explanations and the ability to ask questions) to be essential to their care; nevertheless, less educated patients believed they received too much patient centeredness in comparison to more educated patients. Less educated patients rated these characteristics of patient-centred care as less important than more educated patients (ORs ranged from 0.53 to 0.84 for low vs. high education; ORs ranged from 0.83 to 0.95 for medium vs. high education) as they feel less confident on their health literacy and more likely to be passive recepient of care. However, it is recommended that clinicians should place a greater emphasis on patient-centered regardless of their patient's education level.[32]

Those who were not happy with the consultation duration scored lower mean of overall patient satisfaction (p = 0.006). Patient satisfaction depends on how long the patient perceives the consultation to have lasted. Their expectation of the consultation length and positively experienced consultation often overestimate the time spent with the physician. Thus, the perceived consultation time is vital in determining patient satisfaction.[33] Anderson et al. found that time spent with the physician was the strongest predictor of patient satisfaction. The decrement in satisfaction is substantially reduced with the increase in time spent with the physician[34] however, the actual length of consultation was not responsible for improving patient satisfaction, but rather psychosocial needs and expectation exploration was much more critical.[35]

Due to restricted consultation time, clinicians in a busy clinic may struggle to identify their patients' agenda; therefore, it is vital to ensure that quality consultation time is spent by managing patient expectations and psychological needs. Web-based, electronic medical records with an integrated patient agenda tool that defines the patient's agenda prior to clinic visits may improve the patient's consultation experience at KKBK. Being able to view a patient's agenda prior to an appointment on the electronic medical record and in such a convenient manner will allow doctors to assimilate more patient needs prior to a physical consultation, facilitate communication and assist in identifying the patient's problems more effectively.[36]

Our study also found a significant association between overall satisfaction mean and waiting time (p = 0.003). Those who were not happy with waiting time scored lower on the mean overall satisfaction than those who were happy with the waiting time. Lee et al. found that waiting time has consistently been a significant predictor of patient dissatisfaction,[36] and positive communication could alleviate the harmful effects of long waiting times. Long waiting times remain one of the strongest predictors of patient dissatisfaction[37] and Xie et al.[38] found that patients who experienced longer waiting times considered their healthcare service less accessible and less convenient.

Waiting time can be improved by proper triaging and improving on patient flow process. This can be achieved by implementing efficient data management and integrating technology in patient care. Study showed patient satisfaction was higher with Electronic Medical Record (EMR) than paper-based clinic.[39] Since KKBK is paper-based primary care clinic, it is recommended for KKBK to shift toward EMR clinic. EMR systems allow faster patient information access and proper patient care coordination and thus, longer patient consultation time. Utilizing technology in appointment systems may reduce appointment overbooking and identifying the loops in arranging patient care. COVID-19 pandemic had given a massive paradigm on healthcare systems delivery as virtual telehealth can be used to manage chronic stable non communicable disease patient. Stable patient can be seen virtually, thus avoid congestion and reducing waiting time in KKBK. KKBK should thereby focus more on uncontrolled non communicable disease patients as such can be priorities and seen physically in clinic. Studies

showed patients and healthcare providers reported high level of satisfaction with telemedicine. Both patient and healthcare provider reported a desire to continue telemedicine post COVID-19 pandemic; however, preferred virtual consultation rather than telephone consultation.[40]

Strength and Limitations

This study's strength was that it included the highest clinics patient loads in the Kuantan district. This could indicate that the outcome was sufficiently reliable to represent most of the patient satisfaction at the government primary care clinic in Kuantan. However, because the study sample was limited to Kuantan, the results may not be applicable to other states and countries. Other confounding variables such as patient factors (treatment duration, number of visits and treatment history) and other services (physical facilities, supporting staff services, registration and information system) were not included in this study and may have influenced the results.

CONCLUSION

In conclusion, most respondents who attended KKBK were satisfied with the quality of healthcare services they received despite that KKBK had the highest patient loads in Pahang state. Patient education, waiting time, consultation duration contribute to overal patient satisfaction. In the future, a cohort study should be conducted so that the temporal relationship and association between patient satisfaction and healthcare services can be determined with precision. Future research must be conducted by measuring the waiting time and consultation time objectively as soon as KKBK adopts electronic medical records in order to validate our findings on waiting time and consultation time, which are based solely on self perception. Integrating electronic medical record will make KKBK healthcare system more efficient and reduce on waiting time. Waiting time and consultation duration can be further improved by implementing extended office hours, thus improving accessibility and, as a result, reducing waiting time and lengthen consultations duration. Implementing staggered appointments and the need of online booking for walk in cases may avoid congestion during clinic hours. After-hours access via alternative means, such as telephone, email, telemedicine consultation to cater patients needs during odds hours may enhance patient satisfaction. It is hoped that the outcome of this study will aid the KKBK authorities in improving their quality of services in the future.

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ORIGINAL ARTICLE

A 5-year retrospective study of abdominal aortic aneurysm repair in a Malaysian hospital

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ABSTRACT

Introduction: Prevalence and mortality due to abdominal aortic aneurysms (AAAs) have reduced; however, trends in Malaysia are difficult to determine due to the low prevalence and volume of published data. Our aim was to study current trends in AAA treatment in a national referral unit and compare them to previous reports.

Materials and Methods: A retrospective study was conducted on all patients who had AAA repair between 2015 and 2019 in Kuala Lumpur Hospital (HKL). Operating logbooks from the study period were digitised, and details of aortoiliac aneurysm surgery were analysed. We compared these findings to a previous study on AAA treatment conducted in HKL between 1993 and 1995.

Results: Over the course of 5 years, 496 abdominal aortic surgery were performed. There were 451 patients (90.9%) with AAA, whereas 41 patients (8.3%) had mycotic aneurysms. Among patients with AAA, the median age was 70 (IQR 11) and was mostly male (89.3%), whereas inlay repair was the most common technique (n = 395, 87.5%) while EVAR was employed in 36 patients (8.0%). A two proportion z test comparing emergency surgery proportions between our study cohort (56.1%) and the 1993–1995 cohort (39.3%) was significant (p = .017).

Conclusion: There has been a significant increase in the proportion of emergency surgery in HKL. Open surgery remains the most frequent repair technique. The increase in volume likely reflects the accessibility of healthcare, though other factors may play a role. Improvements in outcomes will benefit from research on the standard of care based on prospective data.

KEYWORDS:
aortic aneurysm; abdominal; infected; Malaysia

INTRODUCTION

Abdominal aortic aneurysm (AAA) prevalence has reduced in Europe whereas mortality associated with AAA has also seen a drop which has been attributed to the introduction of screening programmes.[1] There is a dearth of information on AAA repair among Southeast Asians in the literature. This is likely due to the low prevalence of the disease in this region[2,3] and among Asians in general when compared to Western data.[4,5] Most of these data are from East Asia as data from the Indian subcontinent are scarce[6] and the prevalence of AAA is low even among people of South Asian origin in Western populations.[7] Malaysia has a uniquely diverse demography with Malays, 'Orang Asli' and Borneo natives (62.5%) along with people of Chinese (20.6%) and Indian descent (6.2%) constituting 99.3% of the Malaysian population and has historically been a melting pot of ethnic groups.

Kuala Lumpur Hospital (HKL) is the main vascular referral centre in Malaysia and has been providing vascular services since 1993. We are reporting the current profile of AAA patients and surgery and comparing it with the previous cohort studied by Zainal and Yusha between 1993 and 1995.[8] Our objective was to determine if there is a relative difference in abdominal aortic surgery incidence and emergency proportions between these two periods.

MATERIALS AND METHODS

This research received ethical approval from the National Medical Research and Ethical Committee. We conducted a retrospective study of all patients who underwent aortic aneurysm-related procedures from January 2015 to December 2019 in HKL. General and vascular surgery operating logbooks over the study period were retrieved, and all procedural details were digitised. Aortic surgery cases were extracted using the keywords 'aorta', 'aortic', 'AAA', 'EVAR', 'EVAS', 'TEVAR' and each expansion. Inclusion criteria were abdominal and thoracic aortic aneurysms, aortic dissection (AD), penetrating aortic ulcer (PAU) and mycotic aneurysms of the abdominal aorta. Exclusion criteria were thoracic aneurysm, PAU, dissection, and nonaneurysmal aortoiliac occlusive disease. Case notes were retrieved data were analysed using Microsoft® Office Excel® (12.0.4518.1014). The incidence rate ratio was calculated based on the Malaysian population in 1995 (20.1mil) and 2019 (32.8mil)[9] using log Poisson regression in IBM SPSS Statistics (29.0.0.0).

RESULTS

Over 5 years, our department conducted aortic surgery on 496 patients. Most were men (88.9%), and the median age was 70 years (Table I). There were 489 index surgeries performed, with more emergency surgeries (56.0%) compared to elective cases (Table I). We compared these findings to the previous study by Zainal, which reported 56 surgeries over 30 months, of which 39.3% were emergencies.[8] The incidence rate ratio between the aortic surgeries in 1993–1995 and 2015–2019 was 0.374 (95%CI, 0.278 to 0.494, p < .0001) whereas two-proportion z-test showed that the emergency

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Table I: Characteristics of patients treated for abdominal aortic aneurysm in Kuala Lumpur Hospital between 2015-2019 (n=496)

Characteristics (n=496)	No. (%)
Age* (yrs)	70 (11.5)
Male	441 (88.9)
Ethnicity	
Malay	319 (64.3)
Chinese	153 (30.9)
Indians	12 (2.4)
Borneo	8 (1.6)
Others	4 (0.8)
Presentation	
Emergency	278 (56.0)
Asymptomatic	112 (22.6)
Leak	161 (32.5)
Thrombosis	10 (2.0)
Revision of previous repair	8 (1.61)
Disease	
Abdominal aortic aneurysm	451 (90.9)
Mycotic	41 (8.3)
Aortic dissection with aneurysmal degeneration	3 (0.6)
Risk factors (n=296)	
Age* (yr)	70 (11)
Male gender	264 (89.2)
Smoker	214 (71.8)
Creatinine > 150 μmol/L	54 (18.1)

*Data are presented as median (interquartile range).

Table II: Characteristics of intervention and complications for abdominal aortic aneurysm in Kuala Lumpur Hospital between 2015-2019 (n = 496)

Characteristics	No. (%)
Repair technique of AAA (n = 446)	
In-situ	394 (88.3)
Axilo-bifemoral bypass ± aortic ligation	11(2.4)
EVAR	37 (8.1)
ChEVAR	1 (0.2)
Aortic stent	8 (9.0)
Repair technique of mycotic aneurysm (n=41)	
In-situ	17 (41.5)
Axilo-bifemoral bypass ± aortic ligation	19 (46.3)
EVAR	1 (2.4)
Aortic stent	4 (12.2)
Repair technique of abdominal aortic aneurysmal degeneration due to aortic dissection (n=3)	
In-situ	3 (100%)
Revision surgery (n=6)	
Endovascular extension	2
Graft explantation & in situ repair	2
Axilofemoral bypass	1
Ligation of feeding vessels causing endoleak type 2	1
Complications	
Sigmoid ischemia	8 (2.0%)
Acute lower limb ischemia	16 (3.4%)
Inferior vena cava repair ± ligation	3
Laparotomy for acute abdomen	18
Secondary EVAR intervention	4

AAA = abdominal aortic aneurysm; EVAR = endovascular aneurysm repair; ChEVAR = visceral vessel chimney with endovascular aneurysm repair.

surgery proportions of both these time periods were not equal (z = 2.39, p = .017).

Leaking aneurysms constituted 32.5% (n = 161) of the cohort, whereas ten patients (2%) presented with occlusion of aortic aneurysms. In comparison with the proportions of leaking/ruptured aneurysms reported by Zainal (39.3%), there was not a significant difference in proportions between the two studies (z = 1.03, p = 0.304). During this period, we performed 416 *in situ* aortic repairs and 31 axillobifemoral bypasses when *in situ* repair was found to be unsuitable. Endovascular repair or revision was performed in 45 patients, including 38 EVAR and 8 balloon-expandable aortic stent graft (BE). One patient had a renal artery chimney stent during EVAR (Table II).

Most AAA morphology in this study was fusiform (n = 439, 98.4%) and seven patients had PAU. Open inlay repair was

Table III: Abdominal aortic aneurysm repair case series in Malaysia

Study, yr	No.	Study period (months)	Male (%)	Median age (year)	Smoker	Cardiac disease	Chronic kidney disease	Elective surgery (%)	Leak	Elective mortality (%)	Emergency mortality
Pung et al, 1991[27]	58	31	88	68.7	86	18	4	70.7	29.3	2	47
Zainal et al, 1998[8]	56	30	84.7	69	NA	17.7	8.1	60.7	39.3	8.8	59.1
Lakhwani et al, 2003[28]	54	48	92.6	68.5	94.4	35.1	11.1	38.9	61.1	14.3	42.4
Yii KM, 2003[16]	69	36	78.3	67 † 70 ‡	NA	NA	NA	46.4	24.6	6.3	27.0
Current study	496	60	88.9	70	71.8	31.5	18.1	44.0	32.5	9.6§	16.7‖

†Male. ‡Female, § Open abdominal aortic aneurysm repair, ‖Pooled mortality of EVAR and open repair of abdominal aortic aneurysms. NA = not available.

the dominant treatment choice (n = 394, 88.3%) whereas an endovascular approach constituted 10.3% of AAA treatment. Renal artery reimplantation was performed in four patients whereas a ChEVAR was performed in one. All three patients with aneurysmal degeneration of a proximal AD had open repair. Mycotic aortic aneurysms made up 8.3% (n = 41) of the cohort, of which nearly equal number of patients underwent in situ repair (n=17, 41.5%) and extraanatomical bypass and aortic ligation (n = 19, 46.3%), whereas five patients had endovascular exclusion stent grafts (12.2%).

Eight patients required revision of previous aortic repair that was not from our index cohort. Four of these patients presented with leaks, three of whom had a previous endovascular repair. One patient had a type 2 endoleak and had feeding vessels ligated, whereas one patient had a type 1 leak requiring explantation and in situ repair.

We retrieved records from 65.5% (296) of the total number of AAA cases performed in the study period. We found that most of these patients were smokers (71.8%) and 31% had myocardial disease. Elective mortality among asymptomatic patients was 9.6% for open surgery, whereas there was no mortality among elective EVAR. Mortality for emergency aortic surgery was 16.7%.

Complications included sigmoid ischaemia, inferior vena cava injury, and bowel involvement due to aortoenteric fistula (Table II). Nineteen patients from our cohort required a return to theatre for complications, with 57.9% occurring during the same admission. The most common complication requiring additional intervention after open *in situ* repair was lower limb acute ischaemia due to embolus. Sixteen femoral embolectomies and two distal bypasses were performed for patients with open aortic repair (4.5%). Four patients who received EVAR or aortic stent required secondary reintervention, two of whom were from the EVAR cohort of the study period (5.9%). One patient required proximal extension due to a type 1 endoleak, whereas the other patient required iliac angioplasty. Two patients presented with rupture post-EVAR; one had an in situ repair, whereas the other patient had an explantation, aortic ligation, and axillofemoral bypass.

DISCUSSION

Surgery for AAA in Malaysia has increased significantly since 1995. There was not only an increase in the relative incidence of AAA surgery but also an increase in the proportion of emergency surgery. It is likely that the prevalence of AAA in the country has increased, or that AAA was under-diagnosed in the community during the first study period. There was bias in calculating the incidence rate of each study period as we did not take into account the other centres providing similar services and the evolving health care system over the last 2 decades. However, the incidence rate ratio and the proportion of emergency surgery does infer an increase in AAA in the population. The reasons for this are unclear, as smoking trends have decreased among people aged more than 65 years old,[10] and the population has only increased by 63% since 1995.[9] This phenomenon may be contributed by exposure to other risk factor like hypertension or more referrals driven by greater awareness of the disease, improved imaging accessibility at referring centres, and improved perioperative and postoperative care. Reports from China reveal an increase in AAA mortality associated with hypertension,[11] whereas Finnish data suggest that an increased use of statin and antihypertensives may have contributed to a drop in AAA prevalence.[12]

The demographics of patients with AAA in our cohort were similar to those in other Malaysian studies (Table III). The median age of patients was 68–70 years, which is similar to Western data where most screening is offered to men over 65 years.[1] Similarly, most patients had a history of smoking, which is a known risk factor in the pathogenesis of AAA. Our series had a higher rate of chronic kidney disease (CKD) than the other local studies. This correlates with an exponential increase in the prevalence of end-stage renal disease in Malaysia, increasing from less than 200 to more than 1300 per million population over the last 20 years.[13] Although there is no direct association between the incidence of AAA and CKD, the latter is a predictor of mortality in AAA surgery.

The ethnicity of patients in our series was similar to the three previous studies conducted in West Malaysia, whereby Malays were the majority followed by Chinese. This distribution is more likely to be attributed to ethnic density instead of one group being at a higher risk than the other. The Malaysian ethnic landscape is diverse, and there is much heterogeneity within and genetic similarities between ethnic groups, owing to shared ancestry.[14] As Asians generally have a low prevalence of AAA, future research into risk stratification based on ethnicity in this region will unlikely have significant clinical benefits. An efficient and ethical approach to screening patients should be individualised, considering age, smoking history and sex instead of ethnicity.[7]

The incidence of mycotic aortic aneurysms in Asia is reportedly high, reaching 13% in Taiwan.[15] Although our results are similar to the incidence reported by Yii (7.2%).[16] The rate in our series is high compared to the European literature where rates are 0.5-2%.[15] The wide range may be attributed to challenges in diagnosis, including negative cultures in 21–40% of cases. This highlights a challenge in the management of mycotic aneurysms in this region where organisms such as Salmonella sp and Burkholderia pseudomallei are more common than in the West.[17–19]

Open AAA surgery remains the dominant modality in our centre. Our preference for this approach lies with concerns about the long-term durability of EVAR[20,21] along with the cost of treatment due to the financial austerity of the Ministry of Health. We practice prudent patient selection for EVAR suitability with adherence to IFU. Similar reservations contributed to the draft of the NICE guidelines in 2018[22] and reflected in the reducing trends of EVAR in the UK. In 2016, EVAR was performed in 69% of elective surgery[23] and reduced to 59% in 2022.[24] However, EVAR remains the dominant modality for AAA repair in the US, where more than 80% of AAAs are treated with EVAR.[25] These large differences in treatment modality have repercussions on both patient care and surgeon training. A balance between good endovascular and open surgery training is a challenge in any single centre to improve proficiency and competence in these high-risk procedures.

Though mortality has improved compared to the previous Malaysian studies (Table III), mortality among elective open AAA surgery in our series (9.6%) was high compared to national standards elsewhere, such as in the UK, where it is 3.1%.[24] There may be selection bias as some patients operated on the elective list may have been booked without preoperative assessment and optimisation due to symptoms or large aneurysm size. Similar findings were noted by Filipovic et al. in the UK, where mortality rates were 6.8% in 1998-2002, higher than European and American rates in the literature at the time.[26] The NHS has since observed a marked reduction in elective AAA mortality, which is probably linked to improvements in the standard of care and screening introduced in 2009.

We did not have any mortalities among our EVAR patients which is likely due to our strict criteria for an endovascular approach. Though the EVAR numbers were low, this likely pivoted early mortality in the open surgery group, as patients with complex AAA anatomy were more likely to have open surgery.

Measures to improve elective AAA mortality and reduce emergency AAA repair are symbiotic. Apart from performing audit cycles to achieve better standards of care during the perioperative period, other measures may be adopted or studied for feasibility. Improvements in community health care in reducing smoking prevalence and improving blood pressure control have been recommended. Screening in target groups may also result in earlier detection of AAA at smaller sizes, scheduling surgery as an elective procedure and increasing the proportion of EVAR surgery.[11] Feasibility studies for screening and quality assurance will benefit from prospectively collected data.

The limitations of this study are its retrospective nature. We were unable to retrieve 34.2% of the records from the index cohort, resulting in information bias and inability to record granular data of those patients, including mortality. Secondly, we did not capture the long-term secondary interventions of the EVAR cohort because of the relatively short study period and only captured those that required a return to theatre. Thus, type 2 endoleaks, which are treated in the angiography suite of our centre by interventional radiologists, were not recorded.

CONCLUSION

In conclusion, there has been an increase in AAA surgery at our centre, which is likely due to improvements in referrals and healthcare accessibility, but other factors may play a role in driving prevalence. Mortality among elective open AAA is high and most AAA repairs are performed as an emergency. Improvements in outcome will likely be driven by data from registries and improvements in primary health care.

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Appendectomy and asthma: a search for an association in older subjects

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ABSTRACT

Introduction: Studies have shown an association between appendicitis and immune mediated diseases such as ulcerative colitis and multiple sclerosis. Asthma, like the diseases mentioned, is also an immune mediated disease, and hence could possibly be linked to acute appendicitis. In this study, we aim to explore the association between asthma and appendicitis, using appendectomy as a marker for appendicitis.

Materials and Methods: Individuals 40 years and older with asthma were recruited from an online patient database from UiTM Medical Centers at Selayang and Sungai Buloh. The subjects were interviewed face to face or by telephone. Patients with a history of appendectomy were identified and prevalence of appendectomy was then compared to that of controls of similar age group. The diagnostic criteria from National Asthma Education and Prevention Programme were used to identify individuals suffering from asthma. Controls were sampled from the general population. From both control and asthma groups we excluded persons who knew that their appendix had been histologically normal, and those who had undergone appendectomy as part of some other procedure. Individuals suffering from respiratory diseases other than asthma were also excluded, to prevent confusion of diagnosis.

Results: Twenty-five of the 235 asthma patients had a history of appendectomy (10.6%). Of 1245 controls, 70 had a history of appendectomy, giving an overall prevalence of 6.3%. Gender did not vary in the appendectomy/ no appendectomy groups. Malay subjects had a lower prevalence of appendectomy (3.6%), while Indian subjects had the highest prevalence (13.5%). After partialing out the effects of ethnicity by logistic regression, the adjusted odds ratio between asthma and control subjects was 2.040 (95% CI: 1.216 – 3.420, p = 0.007). This shows a statistically significant association between asthma and appendectomy in this population.

Conclusion: A positive association exists between asthma and appendectomy in a population of subjects 40 years and older. This association is similar to that seen with multiple sclerosis but is the opposite to that seen with ulcerative colitis. The cause of this association needs study, particularly the possibility that an altered microflora has a role to play in mediating both conditions.

KEYWORDS:
Appendicitis; microflora; microbiome; autoimmune diseases; immune system diseases; gastrointestinal diseases; respiratory diseases; microflora hypothesis

INTRODUCTION

Asthma is a hyperactive airway disease that is mediated by an overactive immune system.[1] While it is known that an altered immune system is involved in the development of asthma, the exact factors contributing to such a state have not been well studied. Genetic factors are important, but the literature suggests that environmental factors play a more significant part.[2] The "hygiene hypothesis", proposed since 1958,[3-5] claims that early life infections exert a protective effect against the development of allergy and atopic diseases such as asthma.

Appendicitis, too, may have some etiological relationship with hygiene changes. Barker and others[6,7] have proposed that the introduction of plumbing in the 1980s led to improved hygiene, altered immune responses, and an ultimate increase in appendicitis.

If improved hygiene influences the development of both disorders, it may be possible to show a positive epidemiological correlation between the two conditions.

There are other reasons to suspect that there might be an association between the two conditions. They both occur in younger individuals, show a seasonal variation, and have

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both seen a rise in incidence over the past half a century.[8] Other chronic autoimmune disorders show association with appendicitis. Multiple sclerosis[9] and rheumatoid arthritis[10] are epidemiologically related to appendicitis. The association between ulcerative colitis and appendicitis is well-established[11,12] The association is strongly negative, meaning that persons who develop appendicitis tend not to go on to ulcerative colitis.

Two papers have recently evaluated asthma itself in association with appendicitis. One paper[13] showed no association except with active asthma, the other paper showed a strong likelihood that patients with asthma would undergo appendectomy.[14]

Most researchers have presumed that it is the appendectomy that precipitates the autoimmune disease.[10,13,15] This has prompted them to look for the onset of the autoimmune disorder in the years following the appendectomy, and compare with a "no appendectomy" population. However, this approach will give wrong results if there is an external factor that causes both appendicitis and the autoimmune disorder, because some persons analyzed as "no appendectomy" might well undergo the procedure later in life. Consequently, it is important to study the association only after the age in older persons, who are unlikely to newly develop appendicitis.

Appendicitis is uncommon after the age of 40,[16,17] implying that after this age a person listed as "no appendicitis" would be truly "no appendicitis" In this study we explored the association between asthma appendicitis, using appendectomy as a marker for appendicitis, in subjects 40 years and older.

MATERIALS AND METHODS

In this case-control study, we recruited persons suffering from asthma above the age of 40 and compared the rate of appendectomy among these individuals to controls. Statistical regression models were then used to identify the presence of a relationship between asthma and appendectomy.

Asthma Subjects

Cases were recruited from the online database of asthma patients from UiTM Medical Centre Selayang and Sungai Buloh. For this study, only individuals 40 and older were considered. The case notes of these patients were carefully screened, and only those satisfying the diagnostic criteria of asthma from the National Asthma Education and Prevention Program18 were included into this study.

Controls

Controls were recruited from the general population through convenience sampling by a large team of research students who interviewed their friends, relatives, neighbors, and passers-by. Individuals above the age of 40 who did not suffer from any form of respiratory disease were interviewed and included as controls.

Interview

Interviews were carried out either through telephonic interviews or face to face conversation. An English / Malay/ Chinese medium was used, depending on the preference of the subjects. A history of appendectomy was inquired. If positive, attempts were made further to clarify if intra-operatively there was presence or absence of inflammation of the appendix. We excluded individuals whose appendix was known to be normal intra-operatively or at histology, or if the appendix was removed as part of another operation. Individuals who declined consent for participating in this study were also excluded.

Statistical considerations

Using the formula shown below, we calculated the sample size necessary for this study:[19]

$$n = \frac{(z_\alpha + z_\beta)^2 (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

For a type 1 error of 10%, we assigned Zα as 1.65, Zβ as 0.84 for a 20% type 2 error (Power = 80%) and p1 (prevalence of appendectomy in the general population) as 0.07. The risk of appendectomy in patients suffering from asthma (p2) was assumed to be either 1/3 or 3 times higher to achieve a 75% effect size.

Since this was an exploratory study, we set the alpha at 0.1 instead of the usual 0.05. This provided us with a minimum sample size of 73, assuming that prevalence of appendectomy in asthmatic patients is thrice that of controls, or 250, assuming that the prevalence is a third that of controls (taking a cue from the previously published paper on MS).[9]

The Chi Squared test analytical method was used for basic comparison of the prevalence of appendectomy between cases and controls. We used binary regression analysis to partial out the effects of confounders like ethnicity.

IBM SPSS (version 25) was used for the analysis of data.

Ethics

Ethical approval from UiTM Research Ethics Committee and MUHREC (Monash University Human Research Ethics Committee) – ID: 13022. This research was also carried out in accord with the Good Clinical Practice guidelines.

RESULTS

Of the 744 patients listed in the database of asthma in UiTM Medical Centre Selayang & Sungai Buloh, only 235 were included into the study. The remaining were excluded for the following reasons: Deceased: n=20, Age < 40: n =138, Having other respiratory conditions / diagnosis of asthma uncertain: n=201, Normal appendix during appendicectomy: n=4, Uncontactable / refused to consent for this study : n = 146

We were able to recruit 1265 controls (Table I). Twenty of these had a concurrent respiratory illness, which may or may not have been asthma, and were therefore excluded.

Table I: Characteristics of Cases and Controls

Demographics		Asthma (n = 235)	Controls (n = 1245)	Total (n = 1480)	Appendectomy (n= 104)
Gender	Male	81 (34.5%)	625 (51.2%)	706 (47.7%)	50 (0.07%)
	Female	154 (65.5%)	620 (49.8%)	774 (52.3%)	54 (0.07%)
Average age (years)		60.4	54.2	55.1	
Ethnicity	Malay	179 (76.2%)	468 (37.6%)	647 (43.7%)	35 (0.05%)
	Chinese	13 (5.5%)	566 (45.5%)	579 (39.1%)	37 (0.06%)
	Indian	38 (16.2%)	196 (15.7%)	234 (15.8%)	31 (0.13%)
	Others	5 (2.1%)	15 (1.2%)	20 (1.4%)	1 (0.05%)

Table II: Association between asthma and prevalence of appendectomy

	Appendectomy status		Odds Ratio	P value
	Appendectomy	No appendectomy		
Asthma	25 (10.6%)	210	1.757 (95% CI: 1.095 – 2.820)	0.018
Control	79 (6.3%)	1166		
Total	104 (7.6%)	1376		

Chi Squared = 5.5764, p=0.0182 at 2 degrees of freedom.

Table III: Factors associated with prevalence of appendectomy using multiple logistic regression (n = 1480)

	B	SE	Wald	df	Sig	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Ethnicity (Malay)			17.398	3	0.001			
Ethnicity (Chinese vs Malay)	0.401	0.263	2.325	1	0.127	1.494	0.892	2.501
Ethnicity (Indian vs Malay)	1.085	0.265	16.784	1	0.000	2.961	1.761	4.976
Ethnicity (Others vs Malay)	-0.062	1.044	0.004	1	0.953	0.940	0.122	7.269
Asthma vs Control	0.713	0.264	7.306	1	0.007	2.040	1.216	3.420
Constant	-3.107	0.206	227.204	1	0.000	0.045		

Variable(s) entered on step 1: Age, Ethnicity, Group [asthma or control]
*Backward LR Multiple Logistic Regression statistical method is used.

B: Beta coefficient for the constant in the null model
SE: Standard error around the coefficient for the constant
Wald and Sig: The Wald chi-square test that tests the null hypothesis that the constant is 0.
df: Degrees of freedom for the Wald chi-square test
Exp(B): Exponentiation of the B coefficient, which is also Odds Ratio.

Naegelkerke R squared value: p = 0.036. Hosmer-Lemeshow test, (p = 0.739), classification table (overall correctly classified = 93.0%), and area under ROC curve (63.6%) was applied to test the fitness of this model.

Rates of appendectomy in Cases
Twenty-five of the 235 asthma patients had a history of appendectomy (10.6%) (Table II).

Rates of appendectomy in Controls
Of the 1245 controls, 79 had a history of appendectomy, giving an overall prevalence of 6.3% (Table II). Malay subjects had the lowest rate of appendectomy (3.6%), while Indian subjects had the highest prevalence (13.5%) (Table I).

Association of Asthma and prevalence of Appendectomy
A history of appendectomy was higher among asthmatic subjects when compared to controls. (Odds ratio: 1.795 [95% CI: 1.095 – 2.92], p = 0.018).

Analysis of possible confounding factors
To correct for variations in prevalence caused by confounders, we used logistic regression to further analyze our data. Simple logistic regression showed that ethnicity, but not age and gender influenced the prevalence of appendectomy.

Using binary logistic regression analysis, we were able to partial out the effects of ethnicity on the rates of appendectomy (Table III). As shown in Table I, the prevalence of appendectomy for appendicitis is 1.5 times among Chinese and 2.96 times among Indian patients when compared to that of Malay subjects. After partialing out the effects of ethnicity, the adjusted odds ratio between asthma and control is 2.040 (95% CI: 1.216 – 3.420, p = 0.007).

DISCUSSION

There are only two other publication that investigate the relationship between asthma and appendicitis. The first research was carried out by Hasassri et. al[13] and was published in 2017. This was a population-based case control study attempting to explore the relationship between asthma

and appendicitis among children. Hasassri et al[13] found no difference in a history of asthma between cases and controls, but they did find that appendicitis was more common among patients suffering from active asthma when compared to patients with inactive asthma (OR: 2.58) While the results obtained from Hasassri et al[13] were similar to ours, that study was confined to children. Many of their asthma patients would have been analyzed as "not associated with appendicitis" when in fact they might have developed appendicitis later in life.

The second research was carried out by Kim et al[14] and published after we initiated our own study. Their approach was very similar to ours, in that they did not presume that the immune disease, asthma, was a consequence of the appendectomy. They studied the association at all ages, showing an association that increased in significance from p=0.032 in younger individuals to p=0.002 in the age group 40-59 years. In that respect, our paper confirms their findings, that the association between appendectomy and asthma is more evident in older individuals.

So, what is the likely cause of this apparent association between appendectomy and other diseases (Table IV)? One possible explanation, based on a probable alteration of the gut microflora, is the "hygiene hypothesis".[20] It suggests that infections early on in life play an important a role in immune modulation and immune tolerance, which may prevent the development of auto-immune and allergic diseases such as asthma.[5] Only infections transmitted through the feco-oral route provide such a protective effect against immune mediated diseases, and it is postulated that the colonic microbiota might mediate the development of asthma and allergic diseases.[21] This idea is further supported by studies suggesting the possibility of a "gut-lung axis". Mouse models showed that certain microorganisms, when present in the gastrointestinal system, could reduce airway hyper reactivity.[22] This explanation would require a microflora-based evidence for the development of appendicitis, and for ulcerative colitis and multiple sclerosis as well. And indeed there is strong evidence that these disorders are in some way caused by gut microbial changes. We have already referred to Barker and others[6,7] whose work suggested that the introduction of plumbing in the 1980s led to improved hygiene and an increase in appendicitis. The sanitation may have resulted in a "microbiome depletion" which led to a hyper-immune state, increasing a person's risk of developing other immune mediated diseases, such as asthma.[23] Appendectomy specimens of individuals who suffered from appendicitis harbored a greater incidence of Fusobacterium.[24-26] Reports indicate that ulcerative colitis is another likely microflora-related disease,[27] as, probably, is multiple sclerosis.[28]

This study has several limitations. Case control studies are prone to recall bias. However, appendectomy is a surgery, a major life event, associated with a very visible scar, and it is unlikely that subjects would forget that it happened. Another weakness of this study is that some subjects would have undergone a negative appendectomy, where the appendix was not truly inflamed. Ideally, histopathological records should be examined to ascertain the diagnosis of acute appendicitis, but this was not feasible for an exploratory study such as ours. However, we believe that this will not significantly affect the result of our study. These days the over 90% of appendectomies are correctly carried out for acute appendicitis.[31] The small margin of error is likely to equally affect both the case and control group.

This study also has several strengths. Our first is the large number of controls we have been able to recruit. Also, since asthma subjects are recruited from a clinic, a thorough examination of case files was possible, ensuring an accurate diagnosis of asthma. Finally, we believe that restriction of recruitment to subjects at or above the age of 40 greatly increases the probability of fairly correctly categorizing patients into lifetime appendicitis and non-appendicitis groups, since only about 10% of appendectomies occur after the age of 40.[17] If we had included younger patients, many more might have gone on to develop appendicitis later in their life, and would have been misclassified in the study as "not appendicitis".

CONCLUSIONS

In a population over the age of 40 years, the prevalence of appendectomy among patients with asthma is higher compared to that of controls, and this data is statistically significant. We believe that such an association is likely to be microflora mediated, but this needs to be confirmed with follow up confirmatory studies. In Malaysia, the prevalence of appendectomy is highest among Indian individuals, and the lowest among Malay subjects.

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ORIGINAL ARTICLE

Development of a novel questionnaire to assess knowledge, attitude and practice towards medical disorders in pregnancy among clinicians

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ABSTRACT

Introduction: Maternal medicine is important and complex. It focuses on the care of mothers with comorbidities or medical disorders during pregnancy. To date, there are limited tools to assess clinicians' knowledge, attitude and practice (KAP) in this field.

Materials and Methods: This study aims to develop and validate a questionnaire measuring the KAP of clinicians towards maternal medicine. Literature reviews, item generation and multiple experts' reviews were conducted during the questionnaire development phase. Convenient sampling was undertaken for this cross-sectional survey. A total of 168 clinicians from one tertiary hospital and three health clinics participated in thepilot testing using the modified questionnaire. In addition, test-retest was performed on 30 participants to examine its reliability, whilst exploratory factor analysis (EFA) was undertaken to determine its construct validity.

Results: This finalised questionnaire contained 36 items with excellent content validity. Pertaining to test-retest reliability, all knowledge domain items showed Kappa values > 0.20, except item K29; attitude domain items overall Cronbach's alpha was 0.787 with corrected item-total correlation > 0.300 and lastly, all items in practice domain achieved intra-class correlation index > 0.700, except P2.5. EFA supported four factor structures, but six items were removed due to the following reasons: cross loading, negative or poor loading factor (< 0.3).

Conclusion: Overall, this instrument has an acceptable psychometric property, content validity, internal reliability and construct validity. It is hope that this questionnaire would be validated in other populations and be used in future research to enrich our understanding of clinicians' KAP towards maternal medicine.

KEYWORDS:
Knowledge, attitude and practice; questionnaire; medical disorders; pregnancy

INTRODUCTION

Maternal medicine is a specialised field that focuses on caring of mothers with pre-existing comorbidities or medical disorders that arise during pregnancy, who are at risk of pregnancy related complications.[1] It is generally regarded as a complicated field as medical disorders and pregnancy have bidirectional interactions, whereby a poorly controlled medical disorders would adversely affect the pregnancy outcomes, while stress and physiological adaptations during pregnancy could potentially exacerbate the underlying disease control.[2]

Due to the complexities of this condition, its management is underpinned by a multidisciplinary approach. The challenge starts before conception and continues with optimisation of disease control during pregnancy. Another pivotal aspect of care encompasses peri-conception medication modification to prevent teratogenic effects on the developing foetus. Furthermore, clinicians should also be cognizant regarding medication safety during lactation in order to prevent adverse complications to the nursing infants.[3,4]

Considering the above, it is evident that management of maternal medical disorders is multi-faceted and challenging. To date, Chuang et al demonstrated knowledge deficits about pregnancy-related risks in women with chronic medical diseases and lack of intent to participate in pre-conception health promotion and pregnancy planning.[5] Yet, little has been done to explore about the level of knowledge, attitude and practice (KAP) towards medical disorders in pregnancy among clinicians. Additionally, majority of the published questionnaires mainly focus on the single disease entity which only serve to provide a limited view towards maternal medicine.[6-8] In view of the foregoing, we undertook this study to develop and examine the validity and reliability of an evaluation instrument towards KAP of medical disorders in pregnancy among clinicians with the inclusion of five common medical disorders in pregnancy.

MATERIALS AND METHODS

Questionnaire Development

This questionnaire was a self-administered English questionnaire and answered by clinicians from both medical

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department from a tertiary hospital and health clinics. It contained two sections, a) the respondents' demographic data and b) the KAP towards maternal medicine. Items to assess the KAP in this questionnaire were identified from systematic review of literature and rigorous discussion among the researchers.

In order to assess the knowledge towards maternal medicine comprehensively, we have included five representative disorders encompassing endocrinology, rheumatology, respiratory, neurology and haematology systems.[9-13] Area of knowledge tested was based on the disease epidemiology, clinical characteristics, natural history, prognostic features and pharmacology focusing on pregnancy as well as lactation compatibility, which was believed to be a part of the core knowledge of maternal medicine.[14]

A total of 34 multiple-choice knowledge questions were designed using 'true', 'false' or 'unsure' response categories. Correct responses to the knowledge question were given a score of 1, and incorrect responses or 'unsure' responses were given a score of 0. The eight attitude statements were designed using a Likert scale. Each statement was scored on a five-point scale as follow: strongly agree, agree, neutral, disagree or strongly disagree. Similarly, the nine practice statements were designed using a five-point Likert scale indicating their frequency of actions towards the practice statements. Item P1 included the answer options of < 10, 11 to 20, 21 to 30, 31 to 40 and > 40; whilst the rest of the items included the answer options of almost always, often, sometimes, seldom and almost never. Overall, high scores would indicate a good KAP towards maternal medicine.

Validation Process

Phase 1: Content validity and face validity

The content validation of this instrument was established by seven experts represented by local endocrinologist, neurologist, pulmonologist, haematologist, family medicine specialist and general physician, as well as non-native academician in maternal health. These experts reviewed the questionnaire independently and rated it based on three criteria: content relevance, representativeness and clarity.

Cognitive debriefing, which aimed to assess the face validation was performed on 10 respondents from different backgrounds ranging from medical officers to medical consultants working in the hospital as well as in health clinics after content validation. During the process, the respondents would be required to provide feedback regarding the appropriateness and clarity of the questionnaire via open-ended discussion. The time taken to complete the questionnaire was recorded.

All the feedback from the content and face validation were reviewed by the researchers. The items were either deleted, edited or remain unchanged after an in-depth discussion among the researchers. If the items were changed based on the expert advice, it would be further reviewed by the respective expert till a consensus was achieved. The final version of the questionnaire which consist of five demographic items, 30 knowledge items, seven attitude items and 11 practice items was pilot tested in the next stage.

Phase 2: Pilot testing (reliability analysis and construct validation)

This single-stage pilot testing was a cross-sectional survey and conducted from August 2021 till November 2021 at a single tertiary hospital and three health clinics located within the Klang district, Selangor, Malaysia. It aimed to examine the item analysis, reliability and construct validity of the questionnaire. The sample size required for a validation study was based on the statistical analysis used. With regards to the exploratory factor analysis (EFA), which was deployed to analyse the construct validity of knowledge items (total = 30), require a minimal sample size of 150 respondents. (Ratio of 5:1; 5 × 30 = 150).[15]

Convenient sampling method was chosen to recruit the clinicians from the four health centres. The inclusion criteria were clinicians working in medical department from the tertiary hospital and all clinicians working in the health clinics. All clinicians of the selected centres who met the inclusion criteria were recruited, except house officers.

Data collection was conducted by visiting each of the centres. The objectives and procedure of the study were explained in detail before written consent was obtained from the respondents. The questionnaire was a guided self-administered questionnaire. The clinician could clarify any doubts with the data collectors while answering with no time restriction. However, they had to complete and return the questionnaire on the same day. In addition, 30 clinicians were requested to participate in the test-retest session. They were informed that they would be approached by the researchers within 14 days period for retest.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 25 was used to conduct the statistical analysis. Both item content validity index (I-CVI) and scale content validity index (S-CVI) were calculated to determine the degree of appropriateness of this instrument in measuring the content intended. Items with I-CVI ≥ 78% were considered as appropriate. On the other hand, items with I-CVI between 70 to 78% would be revised and items with I-CVI less than 70% would be removed.[16] In addition, Kappa index was also calculated to measure the inter-rater agreement that adjusts for chance agreement. Items with Kappa index above 0.74 were considered as excellent, whilst 0.60 to 0.74 were good and 0.40 to 0.59 were fair.[17] Domain S-CVI/average of 0.90 or higher would be considered to have achieved excellent content validity.[18]

In order to examine its construct validity, EFA was employed using a polychoric correlation matrix using Factor Software, Version 12.01.02 dated 22nd December 2021. Tetrachoric correlation was a special case of the polychoric correlation applicable when both observed variables were dichotomous. Polychoric correlation was advised when the univariate distributions of ordinal items were asymmetric or with excess of kurtosis. If both indices were lower than one in absolute value, then Pearson correlation was advised. Factor analysis model for binary variables was applied.[19] The factor structure of the dichotomous questionnaire items was examined using principal components analysis (PCA) and promin rotation which enabled analyses based on a polychoric correlation matrix. In order to determine the number of factors to retain in the scale, parallel analysis was used.

For reliability testing, Kappa index was used for knowledge domains, whilst Cronbach's alpha and intra-class correlation (ICC) index were deployed for attitude domains. Lastly, ICC index was used for practice domains. Kappa values < 0.21 were considered as poor agreement, 0.21 to 0.40 were fair agreement, 0.41 to 0.60 was moderate agreement, 0.61 to 0.80 strong agreement and 0.81 to 1.00 were near complete agreement.[20] Items with Cronbach's alpha score more than 0.80 were very reliable, > 0.60 to 0.80 were reliable, >0.40-0.60 were quite reliable, >0.20-0.40 were rather reliable and 0.0-0.20 were less reliable.[15] In another note, we consider items with ICC values < 0.5 as poor reliability, values > 0.5 to 0.75 as moderate reliability, values >0.75-0.9 as good reliability and values >0.9 as excellent reliability.[17]

RESULTS

Content Validity

For the knowledge domain, five subdomains namely diabetes mellitus, systemic lupus erythematosus, bronchial asthma, epilepsy and thrombocytopenia disorders in pregnancy were developed. There was a total of 34 items in this domain. All knowledge items achieved a satisfactory I-CVI score for relevance, clarify and representativeness. On the other hand, all items reported excellent Kappa values, except item K10, K21 and K22 which reported a good Kappa value. With regards to the attitude domains, all items achieved excellent I-CVI and Kappa values. In the practice domains, all items achieved excellent I-CVI and Kappa values. Also, the S-CVI for the knowledge, attitude and practice domains were 0.994, 1.000 and 0.971 respectively. Overall, majority of the items that achieved good to excellent validity, and they were mainly corrected to improve the grammar, understandability and specificity (Table I).

Face Validity

With respect to face validity, it involved a total of 10 participants from medical department of a tertiary hospital (five medical officers with varying degree of clinical experience, one general physician and two medical consultants), and a health clinic (one medical officer and one family medicine specialist).

The mean time required to complete the questionnaire was approximately 7 minutes and all commented that the questionnaire was easy to understand. Of note, one participant commented that P1 response could be influenced by the Coronavirus disease 2019 (COVID-19) pandemic, whilst another participant remarked that the caution should be taken in designing items with binomial response (true vs false) in order to avoid ambiguous items. Nevertheless, the overall comments were positive, and they opined those clinicians with regular exposure to maternal healthcare would be able to answer this questionnaire more confidently.

Pre-Pilot Testing Questionnaire Amendment

For the knowledge domains, item K10, K21 and K22 were deleted due to their comparatively lower Kappa values. Further, item K10 was commented as not a practical question for clinicians working in health clinics or remote setting as anti-double stranded DNA antibodies test are not widely available, item K21 was commented as not specific as the frequency of follow up would largely depend on the disease control and gestational age, and item K22 was commented as too easy. In addition, item K13 was commented as not clear as the aspirin dose was not defined and most clinicians do not practise prescribing aspirin as pre-eclampsia prophylaxis in mothers with SLE. Item K1 was deleted to reduce to total number of items in the final questionnaire.

In the attitude domain, item A7 was deleted in order to reduce to total number of items in the final questionnaire. With regards to the practice domain, item P1 and P9 were deleted from the practice domain to reduce the total number of items due to concern about fatigue bias.

Demographic Profile

A total of 168 respondents participated in the pilot study, represented by clinicians from four healthcare centres, namely Tengku Ampuan Rahimah Hospital (HTAR), Botanik Health Clinic, Pandamaran Health Clinic and Bukit Kuda Health Clinic. The participants were predominantly from HTAR, which constituted 79.2% of the total respondents (n = 133), while the remaining participants were from three health clinics in Klang district (n = 35, 20.8%). The median age of the participants was 32-year-old with a female preponderance, in which 70.8% of them were female gender (n = 119). Majority of the participants were medical officers (n = 127, 75.6%), followed by general physicians (n = 19, 11.3%), subspecialist or subspecialty trainee (n = 17, 10.1%), parallel pathway trainee (n = 2, 1.2%), master programme trainee (n = 2, 1.2%) and family medicine specialist (n = 1, 0.6%). Analysis of the clinical service experience showed that majority of the respondents had clinical service experience of less than 5 years (n = 93, 55.3%) (Table II).

Construct Validity

Item K13 was removed following pilot testing due to ambivalent answer. EFA was applied to determine the factor structure among 29 items related to the knowledge domain. Upon input of the 29 items, K28 was excluded in the analysis by the software due to similarity of item. Several well-known criteria for the factorability of a correlation were used. Firstly, the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.648, above the suggested value of 0.6, and Bartlett's test of sphericity was significant ($\chi 2_{(378)} = 1805.6$, $p < 0.05$). In the current study, all loading factors were above 0.3. The results of EFA on all 28 items extracted four factors based on the parallel analysis. The Eigenvalues and total variance explained by the four factors is shown in Table III.

The results after Promin rotation showed that the first factor explained 16.337% of the variance, with the final set including five items after deleting item K3 due to negative factor loading as well as item K30 and K32 in view of cross loading. It is grouped under medication safety during pregnancy.

Following that, the second factor explained 8.077% of the variance, with final set including eight items after deleting item K11 due to cross loading. It was labelled as family planning and breastfeeding compatibility among mothers with medical disorders. The third factor explained 7.244% of the variance, with the final set including five items were

Table I: Content validation of knowledge, attitude and practice domains for medical disorders in pregnancy

Item	Relevance		Clarity		Representativeness		RESULTS
	I-CVI (Item content validity index)	Kappa	I-CVI (Item content validity index)	Kappa	I-CVI (Item content validity index)	Kappa	
		Knowledge domain					
K1	0.857	0.849	0.857	0.849	0.857	0.849	DELETED
K2	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K3	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
K4	1.000	1.000	1.000	1.000	0.857	0.849	VALIDATED
K5	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
K6	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
K7	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K8	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K9	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K10	0.714	0.658	1.000	1.000	0.857	0.849	DELETED
K11	1.000	1.000	0.857	0.849	1.000	1.000	VALIDATED
K12	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
K13	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
K14	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
K15	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K16	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K17	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K18	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K19	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K20	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K21	0.857	0.849	0.714	0.658	0.857	0.849	DELETED
K22	1.000	1.000	1.000	1.000	0.714	0.658	DELETED
K23	1.000	1.000	0.857	0.849	1.000	1.000	VALIDATED
K24	0.857	0.849	0.857	0.849	0.857	0.849	CORRECTED
K25	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
K26	1.000	1.000	1.000	1.000	0.857	0.849	CORRECTED
K27	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
K28	1.000	1.000	1.000	1.000	0.857	0.849	VALIDATED
K29	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K30	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K31	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K32	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K33	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
K34	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
		Attitude domain					
A1	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
A2	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
A3	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
A4	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
A5	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
A6	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
A7	0.857	0.849	1.000	1.000	0.857	0.849	DELETED
A8	1.000	1.000	1.000	1.000	1.000	1.000	CORRECTED
		Practice domain					
P1	0.857	0.849	0.857	0.849	1.000	1.000	DELETED
P2	0.857	0.849	0.857	0.849	1.000	1.000	VALIDATED
P3	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
P4	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
P5	1.000	1.000	0.857	0.849	1.000	1.000	CORRECTED
P6	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
P7	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
P8	1.000	1.000	1.000	1.000	1.000	1.000	VALIDATED
P9	1.000	1.000	0.857	0.849	1.000	1.000	DELETED

categorised as natural history of maternal medical disorder and pre-pregnancy optimisation among mothers with medical disorders.

Lastly, the fourth factor explained 7.089% of the variance, with the final set including four items which explained the foetal outcome, peri-labour issues and antenatal care. Also, item K19 and K31 due to poor loading factors (<0.3) (Table III).

Reliability

Pertaining to the reliability of this questionnaire, test-retest responses from 30 participants were analysed. Majority of the knowledge items achieved moderate to substantial Kappa value. To note, K8 showed a perfect percentage of agreement, whilst K29 reported low Kappa value, yet the percentage of agreement was 60% and above. Kappa statistical analysis was not applicable to K6, K7, K8, K16 and K20 in view of inability to construct a symmetrical table. Nevertheless, they

Table II: Demographic characteristics of participants

Characteristics	N = 168
Age in years, median (IQR)	32 (8)
Male gender, n (%)	49 (29.2)
Place of practice, n (%)	
Tengku Ampuan Rahimah Hospital	133 (79.2)
Botanik Health Clinic	12 (7.1)
Pandamaran Health Clinic	12 (7.1)
Bukit Kuda Health Clinic	11 (6.6)
Present designation, n (%)	
Medical officer	127 (75.6)
General physician	19 (11.3)
Subspecialist/trainee	17 (10.1)
Parallel pathway trainee	2 (1.2)
Master programme trainee	2 (1.2)
Family medicine specialist	1 (0.6)
Clinical service experience, n (%)	
Less than 2 years	53 (31.5)
2 to less than 5 years	40 (23.8)
5 to less than 10 years	31 (18.5)
10 years and above	44 (26.2)

IQR, Interquartile range

demonstrated a more than 83% of agreement in during the test-retest (Table IV).

In the attitude domains, A2 and A8 were deleted due to low reliability. The final Cronbach's alpha value of this domain was 0.787, suggesting adequate internal reliability. In addition, the corrected item total correlation ranged between 0.352 to 0.801, which were more than 0.3 indicating all the items have adequate correlation with the total score of the domains.[21] This was further supported by the ICC coefficients of all the attitude items, which demonstrated moderate to good reliability (ICC>0.5) (Table V).

For the practice domain, all items reported moderate to near complete agreement, except item P5 and P7. Lastly, P2.5 was retained despite the insignificant confidence interval as this question is considered as clinically relevant. In essence, this questionnaire had adequate reliability (Table VI)

The Final Questionnaire

The final set questionnaire contained 36 items as follow: 22 items measuring the knowledge towards medical disorders in pregnancy; five items assessing the attitude of medical disorders in pregnancy and nine items reflecting practice towards medical disorders in pregnancy. Overall, it demonstrated acceptable psychometric properties, and has good validity and reliability towards the construct measured.

DISCUSSION

According to Jolving et al, there had been greater than four-fold increase in maternal chronic disease during pregnancy in Denmark.[22] The most notable contributing factors to this observation are delayed childbearing and increased prevalence of non-communicable diseases among the reproductive age population. Also, with the advent of assisted reproductive technology for sub-fertile couples, this has made conception possible in most women, especially mothers with chronic medical disorders.[23] Hence, the maternal medicine discipline is integral in ensuring the provision of special medical care for this group of mothers who need additional attention compared to their peers without medical disorder.

Maternal medicine has gained a renewed interest among clinicians as well as obstetrician in recent years. Several questionnaires have been developed or adapted to explore the KAP of medical disorders among the clinicians. In this regard, Bolla et al and Appajigol et al reported the existence of knowledge gap in diabetes care among the clinicians, and they concurred there is a need to improve training in the area of diabetes and pregnancy.[24,25] These findings highlight the importance of periodic maternal medicine KAP assessment among clinicians, and to fill the knowledge gap regularly via medical education. To date, most of the published questionnaires regarding maternal medicine only focus on a single disease entity which are inadequate to examine the full spectrum of maternal medicine.[6-8,24,25] Therefore, development of an inclusive instrument assessing the KAP towards important medical disorders in pregnancy is crucial, and our questionnaire had been proven to be capable of measuring these constructs.

A rigorous re-evaluation on the items was performed based on the reliability and EFA results to determine the items to be retained in the final set of questionnaires. Despite having a relatively low Kappa value, item K29 was retained in the final instruments as it was considered as clinically important knowledge pertaining to the natural history of the relevant disorder. Besides, it has achieved an acceptable percentage of agreement (> 50%). In a different note, item K13 was removed following pilot testing. This was by virtue of differing recommendation towards that practice in the present literature. Finally, EFA analysis which was undertaken to examine the construct validation exhibited a good psychometric property of the knowledge domains with the factor loadings ranging from 0.354 to 0.77.

Admittedly, this study was conducted during COVID-19 pandemic, whereby most of the workforce had been diverted to COVID-19 wards and most of the clinic appointments had

Table III: Exploratory factor analysis for knowledge domain

Items	Factor 1	Factor 2	Factor 3	Factor 4	
K4	0.609				Metformin should be discontinued in women who are already on metformin before pregnancy.
K24	0.607				Women on levetiracetam tend to have an increase in serum Levetiracetam level during second and third trimester
K14	0.576				Cyclophosphamide can be safely continued in pregnant mothers with lupus nephritis.
K5	0.548				Pre-mixed insulin is the preferred type of insulin during pregnancy.
K23	0.539				Sodium valproate should be avoided in reproductive-age women considering pregnancy.
K18		0.617			Leukotriene receptor antagonists should be avoided in pregnant mothers with depressive disorder.
K29		0.564			Thrombocytopenia occurs in 8 to 10% of all pregnancies.
K17		0.563			Theophylline therapy is absolutely contraindicated during pregnancy.
K26		0.533			Oral contraceptives are the contraceptive of choice in mothers taking carbamazepine.
K7		0.519			Women with a history of gestational DM should undergo at least annual screening for diabetes.
K34		0.429			In pregnant women with immune thrombocytopenia who require oral prednisolone therapy, the recommended starting dose is generally higher than non-pregnant counterparts.
K12		0.414			Breastfeeding should be avoided in mothers on hydroxychloroquine therapy.
K25		0.354			Mothers on anti-epileptic therapy should be discouraged from breastfeeding.
K15			0.77		Asthma exacerbation is generally less common during second trimester.
K20			0.680		Uncontrolled bronchial asthma is associated with adverse maternal and foetal outcomes.
K6			0.537		Women with essential hypertension should be screened for DM in pregnancy at 24-28 weeks of conception.
K9			0.504		The prognosis of the pregnancy is best when SLE has been quiescent for at least three months prior to conception.
K2			0.428		Women with pre-existing DM who plan for pregnancy should aim for HbA1c < 7.5% pre-conception.
K8				0.766	Antiphospholipid syndrome should be suspected in mothers with SLE who have had recurrent unexplained miscarriages.
K27				0.653	Antiepileptic drugs polytherapy is associated with increased risk of foetal malformation.
K16				0.572	Pregnant women who require oral steroid to achieve adequate asthma control should be follow up in specialist clinic.
K33				0.483	A safe platelet level for spontaneous vaginal delivery has been defined as >50 × 10^9/L.
Eigenvalues	4.574	2.262	2.028	1.985	
Percentage of variance (%)	16.337	8.077	7.244	7.089	

Extraction method: Principal component analysis
Rotation method: Varimax with Kaiser normalisation

been adjourned during the peak of COVID-19 pandemic. Yet, despite the reduced exposure to maternal medicine, all respondents demonstrated a positive attitude and unanimously opined that knowledge towards medical disorders in pregnancy was important and should be incorporated in both undergraduate and post-graduate training.

Of utmost importance, this questionnaire represents the first validated instrument in measuring KAP towards medical disorders in pregnancy that has incorporated five clinically important medical disorders in pregnancy. Furthermore, by having a non-native expert validation in this questionnaire, it reduces possible biases associated with local practice and increases the acceptability of this questionnaire overseas. In addition, the considerably short answering time required provides evidence about the clarify of the questionnaire and also the low probability of fatigue bias among the respondents. Lastly, it provides a validated framework to the researchers in measuring the KAP towards these constructs. Importantly, we believe utilisation of such findings will provide policy makers insight in formulating future medical training programme that would enhance the field of maternal medicine. It is hope that future researchers would continue to validate this instrument in other population, and to consider expanding the number of items by including more medical disorders to be assessed.

Table IV: Reliability testing of knowledge domain for medical disorders in pregnancy

Item	Coefficient of agreement (Kappa)	Percentage of agreement (%)
K2	0.713	86.67
K4	0.632	83.33
K5	0.483	70.00
K6	NC	83.33
K7	NC	86.67
K8	NC	100.00
K9	0.558	70.00
K12	0.600	73.33
K13	0.427	73.33
K14	0.360	73.33
K15	0.358	66.67
K16	NC	96.67
K17	0.490	66.67
K18	0.438	70.00
K20	NC	93.33
K23	0.620	80.00
K24	0.659	80.00
K25	0.284	60.00
K26	0.525	70.00
K27	0.314	76.67
K28	NC	96.67
K29	0.130	60.00
K33	0.453	70.00
K34	0.392	60.00

NC, not calculated (Unable to construct a symmetrical table)

Table V: Internal consistency reliability and intra-class correlation coefficients of the items in the test-retest of attitude domain for medical disorders in pregnancy

Item	Corrected item-total correlation	Cronbach's alpha if item deleted	ICC	95% CI
A1	0.352	0.808	0.744	(0.462, 0.878)
A3	0.382	0.817	0.737	(0.448, 0.875)
A4	0.678	0.713	0.828	(0.640, 0.918)
A5	0.689	0.703	0.847	(0.678, 0.927)
A6	0.801	0.672	0.699	(0.367, 0.857)

ICC, intra-class correlation coefficient; CI, confidence interval

Table VI: Intra-class correlation coefficients of the items in the test-retest of practice domain for medical disorders in pregnancy

Item	ICC	95% CI
P2.1	0.766	(0.508, 0.889)
P2.2	0.803	(0.586, 0.906)
P2.3	0.970	(0.937, 0.986)
P2.4	0.803	(0.586, 0.906)
P2.5	0.519	(-0.011, 0.771)
P3	0.890	(0.769, 0.948)
P4	0.798	(0.576, 0.904)
P6	0.807	(0.594, 0.908)
P8	0.722	(0.417, 0.868)

ICC, intra-class correlation coefficient; CI, confidence interval

CONCLUSION

In conclusion, this instrument has been proven to be a reliable and valid tool in the assessment of knowledge, attitude and practice (KAP) towards medical disorders in pregnancy or maternal medicine. The inclusiveness of this questionnaire lies in the presence of five clinically important diseases in the knowledge domains, which allows a general assessment of one's knowledge towards maternal medicine. Furthermore, the assessment outcomes would enable better informed strategies by researchers, policy makers and clinicians to optimise the care of mothers with medical disorders.

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ORIGINAL ARTICLE

The relationship between infection severity, wound categorization, and foot care in type 2 diabetes mellitus patients with recurring diabetic foot ulcers

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ABSTRACT

Introduction: Research on diabetic foot ulcers (DFU) infection is limited to the first wound. Therefore, this study aimed to evaluate the relationship between wound classification (Wagner and SHID), and foot care against severity infection of DFU recurrent that may contribute to an increased susceptibility to infection among individuals with recurrent DFUs.

Materials and Methods: A cross-sectional design was used in this study involving 245 participants of type 2 diabetes mellitus (T2DM) was conducted at a Kitamura Wound Care Clinic, PKU Muhammadiyah, located in Pontianak, West Kalimantan, Indonesia, between September 2022 and February 2023. The Kruskal-Wallis test was used to assess the relationship between the foot care practices and infection status. A linear regression test to examine the independent risk factors.

Results: Wounds' characteristics regarding foot care practice group were significantly including more than 5 months wound heal from previous wounds ($p = 0.045$), the percentage of wound site on dorsal was higher in the foot care practice group ($p < 0.001$), the percentage had no deformity feet was higher in the foot care practice group ($p < 0.001$), the percentage had no previous amputation feet was higher in the foot care practice group ($p < 0.001$). Also, the percentage had grade three was higher in the foot care practice group ($p < 0.001$), the percentage had grade three was higher in the foot care practice group ($p < 0.001$), and the percentage had mild infection status was higher in the foot care practice group ($p < 0.001$). The predictors of diabetic foot infection were Wagner and SHID classification and foot care ($p < 0.001$, $p < 0.001$, and $p < 0.01$) respectively.

Conclusion: This study demonstrated that foot-care behaviour in diabetic patients in Indonesia is poor. In addition, this study also has shown Wagner grading, SHID grading, and foot-care are predictors of infection in recurrent DFUs.

KEYWORDS:
Diabetic foot; diabetic foot infection; recurrent; predictor

INTRODUCTION

According to International Diabetes Federation (IDF) data, the number of diabetes mellitus (DM) patients in Indonesia is expected to increase to 16.7 million by 2045, up from 10.3 million in 2017.[1] According to these estimates, Indonesia will rank as the sixth-highest country in terms of the number of DM cases worldwide.[1] This raises worries regarding an increase in diabetic foot ulcers (DFUs), one of the consequences of diabetes.

DFUs are one of the most common problems in diabetics. These ulcers can cause physical limitations and a decrease in DM patients' quality of life.[2–4] Additionally, DFUs exhibit an increased risk for infection, with varying degrees of severity.[5] Infections in DFUs, if not managed appropriately, can lead to more serious complications, such as limb amputation.

Periphery arterial disease (PAD) is a major risk factor for DFUs and a strong risk factor for DFU in diabetics.[6,7] Nearly half of patients have PAD, which raises the risk of infection, non-healing ulcers and amputations.[8] In addition, neuropathy is one feature of DFU's.[9] The development and progression of infections, ischemic ulcers and gangrene in diabetics is facilitated by the interaction of metabolic variables, immunopathy, diabetic neuropathy and diabetic angiopathy.[10]

Based on a study conducted, it has been determined that the incidence rate of DFU infection is approximately 25.2%.[11] Furthermore, a separate investigation revealed that around 56% of DFUs exhibit signs of infection, with approximately 20% of these cases ultimately leading to the need for lower limb amputation.[12] However, it is worth noting that DFUs have the potential to recur. According to a prior investigation, the prevalence of recurrent infection in DFUs was reported to be 40%.[13]

Identifying an infection is one part of the DFU's assessment that can be done by assessing risk factors for infection and paying attention to signs and symptoms.[13] According to one study, the independent risk factor could happen for DFU patients who were healed between 3 to 12 months, experienced peripheral neuropathy, foot deformity, younger age and female gender, presented deep DFUs, or had a history of DFUs.

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DFUs with infections can interfere with mobility.[14,15] Lack of physical mobility will affect the patient's daily activities. This leads to depression and increased costs, thereby reducing quality of life. Other studies show that patients with DFUs will be more angry, frustrated, depressed and helpless compared to patients with DM.[16–18] Based on some of these studies, it can be concluded that patients with DFU infections can lead to declining quality of life.

Recurrent infections in DFUs imply a more complicated problem. Infections on DFUs imply a more complicated problem. The understanding of factors that contribute to the occurrence of infections in DFUs, particularly recurrence, developing efficient prevention and management methods requires an understanding of the risk variables that contribute to recurrent DFU infections.

Currently, research on risk factors for DFU infection is limited to only the first wound, and no risk factors have been found for recurrent DFU infections. Therefore, the purpose of this study is to evaluate relationship between wound classification, foot-care against severity infection DFUs. As a result, the findings of this study are likely to guide healthcare practitioners in developing effective interventions to reduce the risk of infection in DFUs and to improve the quality of life for DM patients.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional design was used in this study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

This study was conducted on type 2 diabetes mellitus (T2DM) patients registered at the Kitamura Wound Care Clinic, PKU Muhammadiyah, located in Pontianak, West Kalimantan, Indonesia, between September 2022 and February 2023.

Study Participants

The sample selection is based on the non-random criteria, and not every person/individual of the population has a chance of being included. A few parameters were used to calculate the sample size and the estimated sample size for this study was 245 participants, and used sample size calculation by Raosoft.[19] The inclusion criteria are above age 18 years with result of grade 2 to 4 Wagner system. Participants who did not match the specified criteria were excluded from the study. Before beginning the study, informed consent was properly obtained from each patient's family. Patients that were excluded from the study were those who had physical limitations, cognitive or neurological impairments, and serious illnesses or consequences.

Observational data

The demographic questionnaire consisted of information such as age, gender occupation and medical history. The clinical information include body mass index, glycemia status, smoking habits, alcohol consumption, treatment methods neuropathy status assessed using the 10 g (5.07 Semmes-Weinstein) monofilament, ankle-brachial index (ABI) and foot care behaviour evaluated using the Nottingham Assessment of Functional Footcare (NAFF). The validity and reliability test results obtained the value of r = 0.357–0.765 and the Cronbach alpha value obtained was 0.791.[20] The clinical data encompassed several aspects related to the wounds, such as their duration, location, presence of foot deformity and history of prior wound healing. The severity of the wounds also was assessed using SHID.[21] SHID classification includes the first classification describes the superficial area that covers the dermis and/or epidermis layer. The second classification includes only the presence of one or more indications or symptoms of an infection and/or inflammation, such as osteomyelitis or ischaemia. The third classification includes tissue damage that affects the subcutaneous layers of the lower dermis and extends to tendon tissue, excluding bone. The fourth classification covers tissue damage areas including subcutaneous, muscle, fascia/tendon and those with one or more indications of osteomyelitis, ischemia, infection or inflammation. The fifth classification includes damage to all skin tissue that penetrates the bone, including tissues that have experienced both localised and severe gangrene. With the inclusion of any one or more of the following indicators, the sixth classification is comparable to the fifth classification: osteomyelitis, inflammation, infection and ischemia.[22] SHID has previously studied the content validity and reliability of this tool, which were 0.72[21] and 0.81[22] respectively. Also, in this study we used the Wagner classification. The Wagner classification system is an early framework for classifying DFUs. It evaluates the depth of the ulcer and the presence of osteomyelitis or gangrene and divides the ulcers into six levels.[23] In order to assess the extent and severity of the infection, the researcher collaborated with a team of qualified wound-care specialists.

Ethical considerations

The study was approved on Feb 23th 2023 by The Institute of Technology and Health of Muhammadiyah West Kalimantan committee with serial number No. 61/II.I.AU/KET.ETIK/III/2023.

Data analysis

Descriptive statistics were performed to identify the categorical variables. The Kruskal-Wallis test was used to assess the relationship between foot care practices and infection status. For the independent risk factor, binary logistic regression test is used to estimate the relationship between wound classification (Wagner and SHID), and foot-care against severity of diabetic foot infection. Data were analysed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA), and $p < 0.05$ was chosen as the level of significance.

RESULTS

Foot care practice

Table I findings indicated that 175 participants examined their feet, while 207 participants checked their shoes before putting them on. While checking shoes when taking them off, 199 participants were checking their feet. 194 participants were washing their feet, while 105 participants were drying their feet after washing them, drying between toes were 178 participants, using moisturising cream on feet were 42 participants, cutting toenails were 79 participants,

Table I: Foot care practice by Nottingham assessment of functional footcare (n = 254)

Variables	F	%
Frequency examining feet		
More than once a day	98	40.0
Once a day	77	31.4
2-6 times a week	58	23.7
Once a week or less	12	4.9
Checking shoes before put them on		
Often	118	48.2
Sometimes	89	36.3
Rarely	31	12.6
Never	7	2.9
Checking shoes when take them off		
Often	102	41.6
Sometimes	97	39.6
Rarely	38	15.5
Never	8	3.3
Frequency washing feet		
More than once a day	124	50.6
Once a day	68	27.7
Most days a week	44	18.0
A few days a week	9	3.7
Drying feet after wash		
Often	105	54.1
Sometimes	70	36.1
Rarely	17	8.8
Never	1	0.5
Drying between toes		
Always	75	30.6
Often	103	42.1
Sometimes	11	4.5
Never	56	22.8
Frequency using moisturising cream on feet		
Daily	15	6.1
Once a week	27	11.0
About once a month	124	50.6
Never	79	32.3
Cutting toenails		
About once a week	20	8.2
About once a month	59	24.1
Less than once a month	153	62.4
Never	13	5.3
Wearing shoes with lace-up, Velcro or strap fastenings		
Most of the time	48	19.6
Sometimes	102	41.6
Rarely	69	28.2
Never	26	10.6
Wearing pointed-toes shoes		
Most of the time	13	5.3
Sometimes	106	43.2
Rarely	56	22.9
Never	70	28.6
Wearing artificial fibre socks		
Most of the time	17	6.9
Sometimes	93	37.9
Rarely	95	39.0
Never	30	12.2
Wearing shoes without socks/stocking/tights		
Never	16	6.5
Rarely	63	25.7
Sometimes	130	53.1
Often	36	14.7
Using a dry dressing on a blister when get one		
Never	53	21.6
Rarely	120	49.0
Sometimes	51	20.8
Often	21	8.6
Foot care practice		
Good	80	32.6
Poor	165	67.4

Data were presented frequency and percentage

Table II: Participants' characteristics regarding foot care

Characteristics	Foot care practice		Total	p value
	Good (n = 80)	Poor (n = 165)		
Sex, no. (%)				0.012*
Female	51 (39.8)	77 (60.2)	128	
Male	29 (24.68)	88 (75.2)	117	
Age, years (%)				0.004**
< 30	14 (93.3)	1 (6.7)	15	
31-39	9 (29.0)	22 (71.0)	31	
40-49	10 (20.8)	38 (79.2)	48	
>50	47 (31.1)	104 (68.9)	151	
BMI, kg/m^2 (%)				0.562
<18.5	4 (25.0)	12 (75.0)	16	
18.5-24.9	42 (30.9)	94 (69.1)	136	
25.0-29.9	28 (38.9)	44 (61.1)	72	
>30	6 (28.6)	15 (71.4)	21	
Duration of DM (years)				0.809
<1	7 (29.2)	17 (70.8)	24	
1-5	39 (35.5)	71 (64.5)	110	
6-10	22 (32.4)	46 (67.6)	68	
>10	12 (27.9)	31 (72.1)	43	
Married status, no (%)				<0.001***
Married	63 (30.7)	142 (69.3)	205	
Widow	2 (8.7)	21 (91.3)	23	
No	15 (88.2)	2 (11.8)	17	
Occupation status, no (%)				0.032*
Civil service	14 (58.3)	10 (41.7)	24	
Private	28 (35.4)	70 (64.6)	98	
Housewife	30 (32.6)	62 (67.4)	92	
Retired	6 (22.2)	21 (77.8)	27	
No	2 (50.0)	2 (50.0)	4	
Education level, no (%)				0.012*
Undergraduate	0 (0.0)	22 (100.0)	22	
Diploma	11 (35.5)	20 (64.5)	32	
Senior high school	2 (20.0)	8 (80.0)	10	
Yunior high school	22 (32.4)	46 (67.6)	68	
Elementary school	45 (39.8)	68 (60.2)	113	
Blood sugar check routinely, no (%)				0.646
Yes	64 (32.0)	136 (68.0)	200	
No	16 (35.6)	29 (64.4)	45	
Smoking, no (%)				<0.001***
None	73 (39.0)	114 (61.0)	187	
Smoker	7 (12.1)	51 (87.9)	58	
Alcohol consumption, no (%)				<0.001***
Yes	1 (3.0)	32 (97.0)	33	
No	79 (37.3)	133 (62.7)	212	
Physical activity routinely, no (%)				0.515
Yes	45 (31.0)	100 (69.0)	145	
No	35 (35.0)	65 (65.0)	100	
Comorbid, no (%)				0.718
Yes	48 (33.6)	95 (66.4)	143	
No	32 (31.40)	70 (68.6)	102	

BMI, body mass index; DM, diabetes mellitus; n, number of participants; *p < 0.05, **p < 0.01, ***p < 0.001

wearing shoes with lace-up, Velcro or strap fastenings were 150 participants, wearing pointed-toes shoes were 119 participants, wearing artificial fibre socks were 110 participants, wearing shoes without socks/stocking/tights were 166 participants, using a dry dressing on a blister when get 72 participants. Regarding foot care practice, 80 participants were good and 165 participants were poor.

Participants' characteristics regarding foot care

A total of 245 patients participated in the present study were identified using non-probability-purposive sampling techniques, consisting of all individuals who had DFUs (Figure 1). The participants' characteristics are summarised in Table II. We found that participants in foot care practice group were significantly older than those without (p = 0.004), female were more common in the foot care practice group (p = 0.012), the number of married participants was higher in the foot care practice group (p < 0.001), the number of participants with private worker was higher in the foot care practice group (p = 0.032), the number of participants with elementary school was higher in the foot care practice group (p = 0.012). Also, the number of participants with no smoking

Table III: Wounds' characteristics regarding foot care

Characteristics	Foot care Practice		Total	p value
	Good (n = 80)	Poor (n = 165)		
Wound onset from previous wound, years (%)				0.192
<1	12 (22.6)	41 (77.4)	53	
1-5	45 (34.4)	86 (65.6)	131	
>5	23 (37.7)	38 (62.3)	61	
Month from last ulcer healed, no (%)				0.045*
< 1	1 (9.1)	10 (90.9)	11	
1-5	18 (25.4)	53 (74.6)	71	
>5	61 (37.4)	102 (62.6)	163	
Wound site, no (%)				<0.001***
Toe	31 (47.7)	34 (52.3)	65	
Metatarsal	18 (40.0)	27 (60.0)	45	
Dorsal	12 (20.0)	58 (80.0)	70	
Heel	1 (8.3)	11 (91.7)	12	
Plantar	16 (20.0)	37(80.0)	53	
Neuropathy, no (%)				0.101
Yes	51(29.5)	122 (70.5)	173	
No	29 (40.3)	43 (59.7)	72	
PAD, no (%)				0.354
Yes	46 (30.5)	105 (69.5)	151	
No	34 (36.2)	60 (63.8)	94	
Deformity feet, no (%)				<0.001***
Yes	4 (9.3)	39 (90.7)	43	
No	76 (37.6)	126 (62.4)	202	
Previous amputation, no (%)				<0.001***
Yes	5 (10.6)	42(89.4)	47	
No	75 (37.9)	123 (62.1)	198	
Wagner grading, no (%)				0.001**
Grade 1	19 (55.9)	15 (44.1)	34	
Grade 2	15 (34.1)	29 (65.9)	44	
Grade 3	46 (30.5)	105 (69.5)	151	
Grade 4	0 (0.0)	16 (100.0)	16	
SHID grading, no (%)				0.003**
Grade 1	10 (71.4)	4 (28.6)	14	
Grade 2	11 (50.0)	11 (50.0)	22	
Grade 3	50 (31.6)	108 (68.4)	158	
Grade 4	5 (20.8)	19 (79.2)	24	
Grade 5	4 (14.8)	23 (85.2)	27	
Infection status, no (%)				<0.001***
Heavy	7 (11.5)	54 (88.5)	61	
Mild	73 (39.7)	111 (60.3)	184	

PAD, peripheral arterial disease; N, number of participants; *p < 0.05, **p < 0.01, ***p < 0.001,

Table IV: Multivariate binary logistic regression analysis relationship between Wagner and SHID classification, and foot care to severity of infection in diabetic foot ulcers (n = 254)

	B	S. E.	Wald	df	Sig.	Exp(B)
Wagner	2.511	0.534	22.144	1	<0.001***	12.321
SHID	1.626	0.251	42.052	1	<0.001***	5.084
Footcare	1.382	0.412	11.240	1	0.001**	3.983
Constant	-14.193	2.058	47.558	1	<0.001***	0.000

** p < 0.01; p<0.001***

(p < 0.001) and alcohol consumption (p < 0.001). Therefore, this study showed that the foot care practice was done by older females with a private worker who had already gotten married, has an education in elementary school, no smoking, and no alcohol consumption.

Wounds' characteristics regarding foot care practice

We found that participants in the foot care practice group were significantly more than 5 months away from healing their previous wounds (p = 0.045), the number of wounds site on dorsal were higher in the foot care practice group (p < 0.001), the number of participants who had no deformities in their feet was higher in the foot care practice group (p < 0.001), the number of participants who had no previous amputation feet were higher in the foot care practice group (p < 0.001). Also, the number of participants who had grade 3 on Wagner classification were higher in the foot care practice group (p < 0.001), and the number of participants

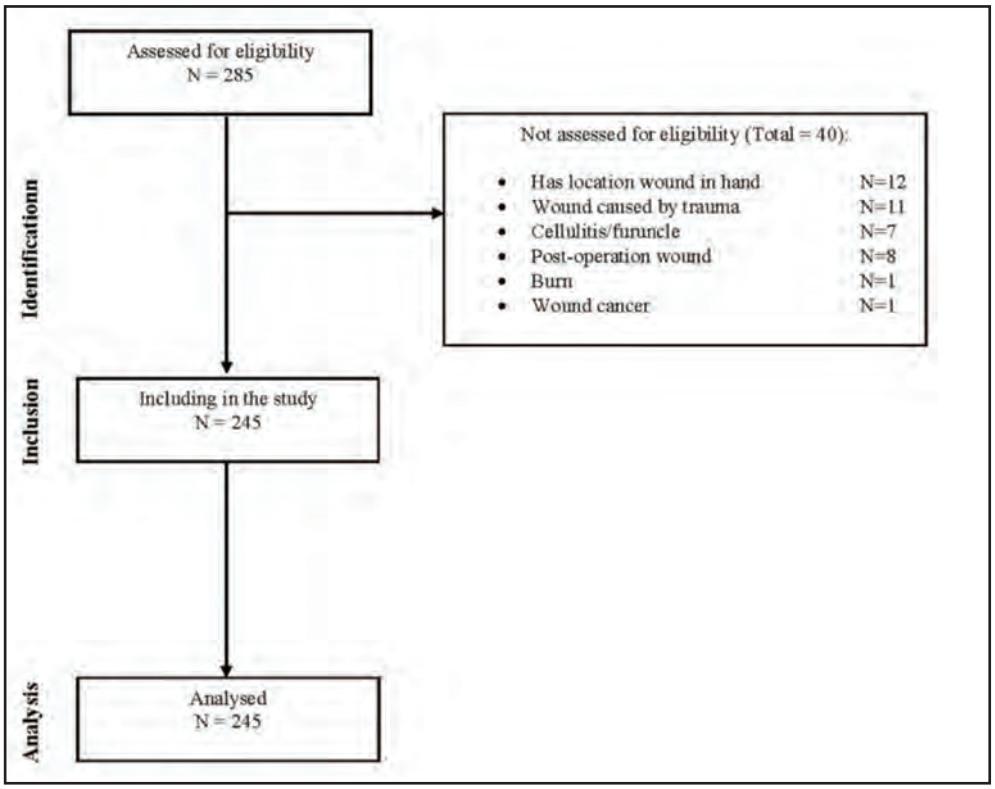

Fig. 1: Strengthening the reporting of observational studies in epidemiology flow chart of the participant enrolment process.

who had mild infection status were higher in the foot care practice group ($p < 0.001$) (Table III). Therefore, this study showed that the foot care practice group were done in a group whose wound healed for more than 5 months at the dorsal location, had no deformity on the foot, had a grade 3 on Wagner classification, and had a mild infection.

Predictors of the severity of infection in DFU

A binary logistic regression shown there was correlation between Wagner, SHID classification and foot care against the severity of infection in DFUs ($p < 0.001$, $p < 0.01$, and $p< 0.001$) respectively (Table IV).

DISCUSSION

Foot care practice is the most important goal to achieve better DFUs care. Analysis of risk factors for infection in recurrent DFUs and self-care foot practice of T2DM patients.

According to the finding, the risk factors infection on DFUs recurrent in Indonesia were wearing shoes with lace-up, Velcro or strap fastenings and wearing pointed-toes shoes. To the best of our knowledge, this is the first study to determine and investigate the factors that may contribute to an increased susceptibility to infection among individuals with recurrent DFUs.

According to the finding, 80 (32.6%) participants with DM had good diabetic foot self-care and consistent with the study of Ethiopia (39.8%).[24] The prevalence of diabetic foot self-care was lower than in Iran (51.4%),[25] and Malaysia (40.4%).[26] However, this is higher than the study done in Turkey (20.8%).[27] The observed disparities can be attributed to variations in the educational attainment levels of the participants in the study. Previous study reported that the status of foot self-care was influenced by education level.[27,28] Also, there are differences in the outcome variables. For example, the study conducted in Turkey used categories of foot self-care as bad, moderate and good, whereas in our study, self-care practice was categorised as poor or good.

In this study, 71.4% of patients inspected their feet daily or more than once daily. This result is higher than study conducted in Turkey (68.6%)[27], and Malaysia (62.7%)[26] compared with studies in Ethiopia (94.7%).[24] About 192 (77.7%) patients washed their feet daily and more than once daily. This result is higher than the study conducted in Turkey (67.4%)[27] compared with studies in Malaysia 93.8%,[26] and Ethiopia (98.7%).[24] About 207 (84.5%) patients often and sometimes checked their shoes before putting them on, consistent with the study of Malaysia (81.6%).[26] This result is higher than the study conducted in Ethiopia (75.3%),[29] and Turkey (56.3%).[27] About 175 (90.2%) patients often and sometimes dry their feet after washing. This result is higher than the study conducted in Ethiopia (16.5%).[29] About 178 (72.7%) patients always and often dry their feet (between toes) which is consistent with the study of Malaysia (74%).[26] About 42 (17.1%) patients used moisturising cream on feet. This result is lower than the study conducted in Ethiopia (25.5%),[29] Malaysia (45.4%),[26] and Turkey (26.8%).[27] About 79 (32.3%) patients cut their toenails once a week or once a month. This result is higher than the study conducted in Ethiopia (29.6%).[29] About 166 (67.8%) patients often and sometimes wear shoes without socks, which is consistent with

the study of Malaysia (63.3%).[26] However, this result is higher than the study conducted in Ethiopia (34.5).[29] This might be due to the differences in knowledge level and education status. According to a previous study, education status has a significant effect on knowledge.[27] This is because if diabetic patients have good knowledge of foot self-care then they will be able to improve their foot practice.[24]

Our study found that smoking was one of the predictors of diabetic foot infection. The result is consistent that smoking has been identified as a significant risk factor for the development of infections in diabetic foot, largely attributed to its detrimental effects on blood circulation and impaired wound healing.[30–32] A systematic review reported that smoking is a risk factor for the recurrence of DFU.[33,34] In addition, a previous study reported that recurrence was a risk factor for foot infection.[35] Therefore, smoking can lead to the recurrence of DFU, which is a risk factor for infections in DFUs.

Another finding from our study was that deformity of feet is a predictor of diabetic foot infection. Foot deformities in diabetic patients can lead to abnormal pressure distributions, causing ulcerations that are at risk of infection, especially when combined with other complications like neuropathy and impaired circulation. The combination of reduced sensation, abnormal foot structure and compromised blood flow creates a conducive environment for the development and recurrence of infections.[35] This result consistent with a previous study that conducted on patients with recurrent DFUs found a significant association between foot deformity and the occurrence of infections in the ulcers.[36] Therefore, foot deformities play a crucial role in the development and recurrence of DFUs. The combination of pressure abnormalities, reduced sensation, impaired circulation and shoe-fit issues can lead to wounds that are more susceptible to infections. Proper foot care, including addressing deformities and ensuring optimal shoe fit, is critical in preventing complications in individuals with diabetes.

Another finding shown in Wagner and SHID grading was a predictor of diabetic foot infection. This result is consistent with previous study that reported that Wagner grade III/IV was a risk factor for the recurrence of DFUs,[33] and recurrence is a risk factor in diabetic foot infection.[35] As we know, the Wagner grading system is commonly used to classify the severity of DFUs, with higher grades typically associated with more severe complications, including infection. Consistent with our study, the predominant data was for Wagner grades III. Interestingly, both the Wagner and SHID grading results were predominantly at grade III. SHID grading also used to classify the infection of DFU with good validity (0.72%),[21] and reliability (0.81 to 1.00).[22]

The present study has some limitations and strengths. Firstly, due to this study being cross-sectional, it can be difficult to identify the causal factors. Secondly, this study was carried out in Indonesia, results cannot be generalised to other countries. Meanwhile, the strength of this study is less research on DFUs conducted in Indonesia and most of them conducted in the western and middle east countries with different population background, and the first study to reveal that SHID grading is predictor for infection in recurrent DFUs.

Clinical implications

It was important to identify the associated factors of DFUs as early as possible to allow early interventions and develop new practice guideline and strategies. Sufficient knowledge, and information will lead them to decrease an ability to do self-care towards their DFUs. A campaign awareness and educational programs related to foot-care should be implemented as preventive strategies to prevent infections in diabetic foot.

CONCLUSION

This study may contribute to a greater knowledge of associated factors of risk for infection in recurrent diabetic foot ulcers (DFUs) especially type 2 diabetes mellitus in maintaining good health practice. Thus, continued efforts and reminders need to be given to those recurrent DFUs on predictors of infection such as Wagner grading, SHID grading and foot-care.

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ORIGINAL ARTICLE

Usage of vildagliptin among patients with type 2 diabetes mellitus attending a public primary healthcare clinics in Kuala Selangor District, Selangor

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ABSTRACT

Introduction: Studies showed that vildagliptin can lower HbA1c levels by 0.8%–1%. However, there is limited data looking at vildagliptin use among suburban populations. The efficacy of vildagliptin use may differ among different populations, especially those with low socio-economic status. Thus, this study aimed to assess the HbA1c reduction after vildagliptin initiation, treatment patterns and the reason for its initiation among patients with type 2 diabetes mellitus attending outpatient clinics in Kuala Selangor District, Selangor.

Materials and Methods: This is a cross-sectional, retrospective study design. All patients who received vildagliptin in the Pharmacy Integrated Health System (PHIS) registry database from 2016 to 2021 were included as study samples. The exclusion criteria were being less than 18 years old and having type 1 diabetes mellitus. Patients' medical records were retrieved after sampling, and data were collected. One medical record was missing, thus SPSS analysis were performed on 144 vildagliptin users.

Results: In total, 84 females (58.3%) and 60 males (41.7%) with a mean age of 62.1 (±10.1) years were analysed in this study. Mean HbA1c pre-therapy was 8.5 ± 2.1%; while post-therapy 6 months demonstrated a mean HbA1c of 7.9 ± 1.8%. Use of vildagliptin alone or as an adjunct was associated with a mean reduction of 0.6% in HbA1c (p = 0.01). Factors influencing this HbA1c reduction were advancing age, specifically individuals aged 62 years and older (p = 0.02), patients who are already receiving insulin therapy (p=0.00) and those who express a willingness to commence insulin treatment during the counselling session prior to initiating the treatment plan (p = 0.00). Reasons for vildagliptin initiation documented by prescribers were non-insulin acceptance (n = 59, 40.97%), frequent hypoglycaemia (n = 6, 4.1%) and non-compliance with medications (n = 23, 15.9%). There was no association between demographic, medical background and reason for starting vildagliptin variables and HbA1c reduction (p < 0.001).

Conclusion: This study showed that initiating vildagliptin alone or as an adjunct therapy significantly reduced HbA1c and is beneficial for uncontrolled diabetes patients. While advancing age, concurrent administration of insulin and the patients' willingness to accept insulin treatment prior to the commencement of therapy were the factors that influenced HbA1c reduction among patients receiving vildagliptin therapy, we recommend primary care providers prioritise all of the significant variables discovered before initiating vildagliptin for their patients.

KEYWORDS:
vildagliptin; DPP-4 inhibitor; type 2 diabetes mellitus; T2DM

INTRODUCTION

The prevalence of patients with type 2 diabetes mellitus (T2DM) in Malaysia is increasing, from 13.4% in 2015 to 18.3% in 2019.[1] Remarkably, recent data from the National Diabetes Registry found that the prevalence of uncontrolled HbA1c is high compared to the controlled group, with a cut-off HbA1c level of 6.5% and below defined as controlled.[2] Studies showed that poor health literacy, low income and a poor social support population make them more likely to have poor glycemic control.[3,4] Kuala Selangor lies in a suburban area, and the majority of the people work as fishermen, self-employed, hawkers or government servants. The populations represent low to moderate socio-economic status. Data from an internal clinical audit showed that HbA1c levels in Kuala Selangor district mainly range from 7.5% to 8.5%, which is far from the Malaysian glycemic target of HbA1c 6.5%.[5] Thus, different measures are being taken to tackle this issue. These include using a multidisciplinary team approach and frequent audits and quality assurance to ensure the treatment modalities used are cost-effective and valuable to patients making the best use of common oral glucose-lowering drugs (OGLD). Treatment modalities used include metformin, sulphonylurea, Sodium-Glucose Cotransporter-2 inhibitors (SGLT2-i), insulin and DPP-4 inhibitors.

DPP-4 inhibitors prevent the hormone GLP-1 from degrading, which boosts the release of insulin right after a meal. Researchers have found that DPP-4 inhibitors help people reach their treatment goal of a 0.8%–1.0% drop in HbA1c

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with fewer hypoglycaemic side effects and better tolerance in older people.[6,7] With patients receiving a higher dose, the reduction in HbA1c is greater.[7,8] Due to its limited availability in Malaysia, especially in primary care settings, its use is mainly reserved as a second-line therapy among patients inadequately controlled on the maximal tolerated dose of sulphonylurea and contraindicated for metformin therapy or inadequately controlled with dual combination therapy with sulphonylurea and metformin.[8] Since the introduction of DPP-4 inhibitors in Kuala Selangor in 2016, only vildagliptin has been made available to our district health clinics. Other DPP-4 inhibitors have been introduced, but in view of vildagliptin's feasibility of use in terms of drug dosing and needing no-renal dose adjustment, it is still the preferred agent in our local settings. It has been in use up until the completion of this study.

The clinical efficacy of vildagliptin use among diabetic patients has been demonstrated in several studies in the literature review,[9,10] but is limited in Malaysia, especially in suburban populations with low to moderate socio-economic status in Kuala Selangor. Thus, exploring the usage of vildagliptin and its effect on HbA1c reduction, factors that influenced HbA1c reduction among vildagliptin users, treatment pattern and reason for its' initiation among prescribers is important for future reference and guidelines.

MATERIALS AND METHODS

This study is a cross-sectional, retrospective study involving patients' attending public primary healthcare clinics in Kuala Selangor district. All patients who received vildagliptin therapy registered under the Pharmacy Integrated Health System (PHIS) database under Kuala Selangor district from 2016 to 2021 were included in the study sample, while those below the age of 18 and having type 1 diabetes mellitus were excluded. A total of 145 patients were recruited in the sampling frame. Retrieval of patients' records was done from the PHIS database after sampling. Outpatient clinics that were involved during the retrieval of patients' records include Tanjung Karang Health Clinic, Kuala Selangor Health Clinic, Bukit Cerakah Health Clinic, Bestari Jaya Health Clinic, Ijok Health Clinic, Jeram Health Clinic and Sungai Tengi Kanan Health Clinic. Data on demographic and medical parameters, prescribers' documentation on the reason for vildagliptin initiation and changes in HbA1c were collected from the patients' record using a data collection sheet. One record was missing, so 144 patients were entered into the analysis.

Variables and Outcomes

Study variables were demographic characteristics, medical characteristics and the reason for vildagliptin initiation in the study population. The outcomes measured were mean HbA1c reductions post-therapy and variables that influenced HbA1c differences post-therapy for 6 months. Treatment patterns were also described in the analysis.

Data Management and Analysis

IBM SPSS version 26.0 was used for data analysis. Categorical data were analysed using descriptive statistics and reported as frequencies and percentages, while continuous data were reported as mean ± standard deviation (SD). A multivariate analysis (one-way MANOVA test) was used to compare the HbA1c difference between the groups (pre- and post-therapy). Post-hoc analysis (least significant differences) was conducted for significant ANOVA outcomes. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Description and Treatment Patterns

In total, 145 patients received vildagliptin during the study period. One patient's record was missing, thus 84 females (58.3%) and 60 males (41.7%) were analysed (n = 144). The mean age was 62.1 ± 10.1 years old, while the mean duration of diabetes was 12.25 ± 6.7 years. One-third of them were obese (BMI ≥ 30 kg/m^2), while 94.4% had hypertension as a comorbidity. 75.7% have renal impairment, defined as a glomerular filtration rate less than 90 ml/min. The baseline characteristics of patients who were treated with vildagliptin, as well as the relationship between these characteristics and the difference in HbA1c after 6 months of vildagliptin therapy, are described in Table I. Paired t test were conducted to assess HbA1c reduction pre- and post-therapy. The mean HbA1c pre-therapy was 8.5 ± 2.1%, while post-therapy 6 months demonstrated a mean HbA1c of 7.9±1.8%. Use of vildagliptin as alone or as an adjunct was associated with a mean reduction of 0.6% in HbA1c; mean difference –0.6 ± 0.23 SD (–1.05, –0.15 95% CI) (p = 0.01). Factor analysis demonstrated three statistically significant values, which were advancing age, specifically individuals aged 62 years and older (p = 0.02), patients who are already receiving insulin therapy (p = 0.00) and those who express a willingness to commence insulin treatment during the counselling session prior to initiating the treatment plan (p = 0.00). Looking at treatment patterns, 85.5% received dual or triple agents, either in combination with metformin or together with sulphonylureas. Half of them were already on insulin at baseline (54.9%), while others remained on vildagliptin with combination with other agents or alone.

Figure 1 showed mean HbA1c reductions pre- and post-therapy while reasons for vildagliptin initiation were described in Figure 2. Looking at Figure 1, mean age (62.1 ± 10.1 years old) showed a lesser reduction in HbA1c during post-therapy compared to other factors, such as concomitant insulin therapy and patients who can accept insulin prior to initiation of vildagliptin. On the other hand, Figure 2 depicts prescribers' reasons for vildagliptin initiation. The most common reasons given were refusal of insulin therapy (40.9%), noncompliance with medication (15.9%) and frequent hypoglycaemia (4.1%).

DISCUSSION

Local guidelines recommend use of DPP4-inhibitor among patients with HbA1c 6.5%–10% as an alternative or with combination with other oral hypoglycaemic agent like metformin and sulphonylureas.[11] Some patients in this study have HbA1c of more than 10% prior to initiation of vildagliptin. While half of patients in this study refused insulin as stated by prescribers in their medical records, further reason for this issue need to be explored in future research. Many patients were overweight (BMI 23–27.4 kg/m^2), and these findings similar with studies done among

Table I: Demographics, medical characteristics and treatment pattern of study participants and difference in HbA1c level (n = 144)

Demographic characteristics	n (%)	HbA1c (%) pre-therapy	HbA1c (%) post 6 months	p value
Age, years (mean)	62.1 (±10.1)	8.471 ± 2.14	7.87 ± 1.89	0.02*
Weight, kg (mean)	73.4 (±15.5)	8.471 ± 2.14	7.87± 1.89	0.45
BMI, kg/m^2 (mean)	28.6 (±5.6)	8.471 ± 2.14	7.87± 1.89	0.91
Gender				
Male	60 (41.7)	8.05 ± 1.7	7.44 ± 1.5	0.06
Female	84 (58.3)	8.78 ± 2.07	8.19 ± 2.0	
Ethnicity				
Malay	108 (75)	8.52 ± 2.12	7.71 ± 1.67	0.91
Chinese	16 (11.1)	7.36 ± 0.91	7.27 ± 1.73	
Indian	20 (13.9)	9.06 ± 2.65	9.22 ± 2.54	
Employment				
Employed	41 (28.5)	8.493 ± 0.34	7.922 ± 0.3	0.98
unemployed	103 (71.5)	8.463 ± 0.21	7.86 ± 0.19	
Medical characteristics				
Duration of diabetes, years (mean)	12.25 (±6.7)	8.47 ± 2.15	7.87 ± 1.89	0.54
Polypharmacy (five and more drugs)				
Yes	136 (94.4)	8.49 ± 2.15	7.92 ± 1.89	0.46
No	8 (5.6)	8.14 ± 2.21	7.15 ± 1.76	
Renal impairment (eGFR<90 ml/min)				
Yes	109 (75.7)	8.406 ± 2.22	7.75 ± 1.88	0.35
No	35 (24.3)	8.67 ± 1.93	8.26 ± 1.91	
History of stroke				
Yes	1 (0.7)	9.0 ± 0.0	7.6 ± 0.0	0.86
No	143 (99.3)	8.47 ± 2.15	7.88 ± 1.90	
History of coronary artery disease				
Yes	17 (11.8)	8.05 ± 1.89	7.91 ± 2.06	0.39
No	127 (88.2)	8.53 ± 2.18	7.87 ± 1.88	
Obesity (BMI ≥30 kg/m2)				
Yes	49 (34.0)	8.26 ± 1.73	7.79 ± 1.66	0.64
No	95 (66.0)	8.58 ± 2.33	7.92 ± 2.01	
Hypertension				
Yes	136 (94.4)	8.49 ± 2.19	7.93 ± 1.92	0.29
No	8 (5.6)	8.21 ± 1.18	7.04 ± 1.09	
Dyslipidaemia				
Yes	0.29	8.53 ± 2.17	7.93 ± 1.91	0.23
No	6 (4.2)	7.23 ± 0.58	6.59 ± 0.46	
Treatment patterns				
Usage of oral hypoglycaemic agent				
vildagliptin alone	21 (14.6)	8.57 ± 2.51	7.97 ± 2.2	0.07
vildagliptin and metformin	63 (43.8)	9.005 ± 2.55	8.2 ± 2.05	
vildagliptin, metformin and sulphonylureas	60 (41.7)	7.89 ± 1.24	7.51 ± 1.55	
Insulin therapy				
Yes	79 (54.9)	9.25 ± 2.5	8.48 ± 2.06	0.00*
no	65 (45.1)	7.54 ± 1.03	7.15 ± 1.37	
Reason for vildagliptin initiation				
History of non-compliance pre-initiation				
Yes	23 (16.0)	8.78 ± 2.09	8.41 ± 1.72	0.29
No	121 (84.0)	8.41 ± 2.16	7.77 ± 1.92	
History of hypoglycaemia pre-initiation				
Yes	6 (4.2)	8.95 ± 2.53	7.85 ± 0.91	0.69
No	138 (95.8)	8.45 ± 2.14	7.88 ± 1.89	
Insulin acceptance pre-initiation				
Yes	85 (59.0)	9.18 ± 2.42	8.43 ± 2.03	0.00*
No	59 (40.9)	7.49 ± 0.97	7.08 ± 1.38	

*p value <0.05 (significant).

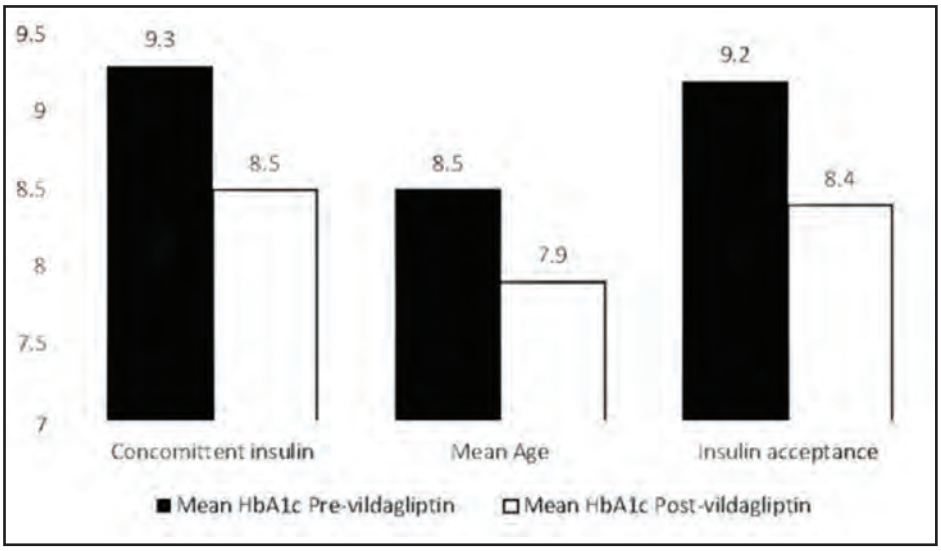

Fig. 1: HbA1c reduction pre- and post-vildagliptin therapy based on factors found on statistical analysis.

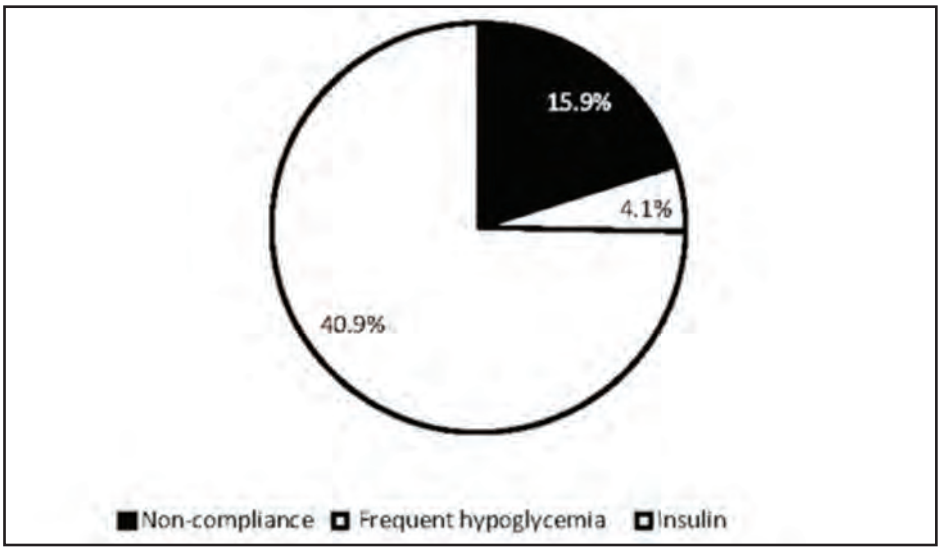

Fig. 2: Reasons for vildagliptin initiation (n = 144).

DPP4-inhibitor users in hospital settings in Malaysia.[12] Dyslipidaemia, followed by hypertension and coronary artery disease (CAD), is most common in our study population. Majority of patients have renal impairment at the start of therapy, probably due to long-standing years of diabetes; mean duration of 12 years. DPP4-inhibitor effectively lowers HbA1c, and meta-analysis have shown its safety among diabetes patients at various stages of renal insufficiency.[13]

The HbA1c reduction rate found in this study is lower compared to other studies done in different populations worldwide. Overall, the reduction rate reported from other studies ranged from 0.8% to 1.0%.4–6 Interestingly, we found that other than age, gender, ethnicity and employment status, they did not have a significant impact on HbA1c, as well as the patients' medical background in this study. There are many factors, like health literacy, that could possibly influence these findings and hence need to be explored. During the analysis, we found that three factors may influence HbA1c reduction after 6 months of vildagliptin initiation: increasing age, patients on concurrent insulin therapy and insulin acceptance prior to treatment.

Increasing Age

According to a study conducted by Hong, Jung[14], was determined that advancing age is an indicator of HbA1c reduction in patients on DPP-4 inhibitor therapy, with a mean age of 53 years. However, the group under study exhibits a contrasting perspective; specifically, the advantages were observed to vary significantly with a 10-year difference in age compared to our study. A systematic analysis also found that a reduction of HbA1c of 8.4% was seen among elderly patients receiving vildagliptin 50 mg bd dosing (65 years old and older) compared to other age ranges.[11] In addition, randomised controlled trials have reported that the elderly significantly reduced HbA1c

compared to the placebo group among those treated with vildagliptin,[12] and they demonstrated fewer hypoglycaemic events during the treatment. Thus, the reduction of HbA1c in this study cannot be negligible and needs to be emphasised during future consultations. Additional variables such as body mass index (BMI) and gender were shown to be statistically insignificant, aligning with the findings reported in the aforementioned study by Mathieu and Degrande.[11]

Patients with Concomitant Insulin Therapy

Most diabetic patients in this study were on insulin therapy (54.9%) concurrent with their vildagliptin treatment. Significant reductions in HbA1c were observed among them after 6 months of initiation compared to those without insulin therapy. Even though a study by Mak, Nagarajah[15] found that adding DPP-4 inhibitors to patients with or without insulin therapy will have a significant impact on the HbA1c level, our study found it differently. However, the specific type of insulin therapy was not addressed in the study, and the HbA1c outcomes were also obtained at varied durations of DPP-4 inhibitors used. Nevertheless, if cost is a concern, it may be advantageous to concentrate on this particular demographic, as previous research has demonstrated its efficacy. Based on systematic studies, using a combination of DPP-4 inhibitors, specifically vildagliptin, along with insulin was suggested as a safe and effective way to improve blood sugar control. In addition, it was shown in the study that vildagliptin reduced HbA1c by 0.8%, with a between-group difference of −0.7% compared with placebo. This method minimises the likelihood of hypoglycaemia or excessive weight gain.[16] In addition, according to Ebrashy et al.[17], adding vildagliptin to insulin reduced HbA1c, body weight and insulin dosage in a clinically significant way without exposing T2DM patients at risk for hypoglycaemia. Additionally, Li et al.[18] found that patients receiving vildagliptin add-on insulin therapy had a significantly lower HbA1c (by 0.9%) than those receiving placebo at the endpoint.

Insulin Acceptance

Interestingly, according to the analysis, a subset of patients was initiated on vildagliptin due to their refusal of insulin. However, the statistical findings revealed the opposite outcome. The results of our investigation indicate that patients who demonstrated a willingness to initiate insulin therapy experienced a notable decrease in HbA1c levels, with a mean reduction from 9.1% to 8.4% (–0.7). Nevertheless, certain individuals who expressed their willingness to initiate insulin therapy after the initial consultation ultimately commenced insulin treatment during the subsequent follow-up session. A qualitative study showed that belief and insulin acceptance do have an impact on medication adherence and glycemic control in the long term run.[19] Insulin acceptance has become one of the major factors for determining target glycemic control among many countries worldwide.[20] However, studies have shown that DPP-4 inhibitors can only lower HbA1c levels by up to 0.8% when used alone.[5] In addition, when taken with insulin, the reduction in insulin requirement is more significant. Hence, the selection of an optimal patient profile and the assessment of readiness for insulin administration are crucial considerations in the context of follow-up care among patients planning to start on vildagliptin therapy.

STUDY LIMITATIONS

This study is a cross-sectional study design; thus, it cannot determine a true causal-effect relationship. As it was done retrospectively, many factors could not be assessed that may have influenced the study findings, such as monthly income of patients (to determine their socio-economic status), and their reasons for insulin refusal. Additionally, there are potential sources of error in the process of transcribing manual prescriptions from the patients' record into the PHIS, which could result in the omission of data. Furthermore, there were other confounding factors that contributed to the decrease in HbA1c levels, apart from the use of pharmaceutical therapy. These factors may have potentially impacted the accuracy of the data reported in the present investigation. Additional variables that could potentially influence the results, such as levels of physical activity, dietary habits and the occurrence of surgical interventions, were not included in the study's measurements.

RECOMMENDATIONS

Despite its several limitations, this study's findings showed that there was a reduction in HbA1c after 6 months of its initiation among vildagliptin users. Therefore, its usage is beneficial and should be recommended to improve glycemic control among people with type 2 diabetes. Addressing age and willingness to start insulin influence positive outcomes, which should be emphasised during clinical consultation. Despite that, we recommend future research with a better study design, such as randomised controlled trials to look for the true effect of vildagliptin on HbA1c reduction and case–control studies to look for the true odds ratio among factors that we found during this analysis. In additon, a qualitative study looking at the reasons for insulin refusal among this population is highly recommended.

CONCLUSIONS

This study showed that initiating vildagliptin alone or as an adjunct therapy significantly reduced HbA1c and is beneficial for uncontrolled diabetes patients. While advancing age, concurrent administration of insulin, and the patients' willingness to accept insulin treatment prior to the commencement of therapy were the factors that influenced HbA1c reduction among patients receiving vildagliptin therapy, and we recommend primary care providers prioritise all of the significant variables discovered before initiating vildagliptin for their patients.

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ORIGINAL ARTICLE

Prevalence and antimicrobial resistance profile of Salmonella typhi infection in Iraq, 2019–2021

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ABSTRACT

Introduction: *Salmonella typhi* could infect the intestinal tract and the bloodstream or invade body organs and secrete endotoxins. It is endemic in developing countries. It is increasingly evolving antimicrobial resistance to several commonly used antimicrobial agents.

Materials and Methods: A cross-sectional study was done at Iraqi Communicable Disease Control Center, where all confirmed cases of *Salmonella typhi* are reported, for a period 2019–2021. All demographic, epidemiological and clinical characteristics of patients, comorbidities, type of samples, distribution of *S. typhi* by age and gender, time distribution in each year and profile of bacterial resistance and sensitivity to antibiotics were gathered and analysed.

Results: Most samples were taken from blood. The mean age of cases during 2019, 2020 and 2021 was 18.7 ± 6.5, 17.7 ± 14.1 and 17.3 ± 12.8. Males constituted 56.7%, 58.5% and 39.8%, respectively. Some cases had comorbidities. Most cases had headache and fever. Some of them had nausea, diarrhoea, vomiting and epigastric pain. The age and sex were significantly associated with years of reporting. The most months of case reporting were June–July (2019 and 2021), Jan. –Feb. (2020). There was an obvious increase in *S. typhi* resistance to ceftriaxone (92.2%, 86.1%, 88.8%) and ampicillin (77.1%, 76.9%, 81.27%). There was a gradual increase in sensitivity to tetracycline (83.1%, 88.1%, 94%), cotrimoxazole (86.7%, 86.1%, 92.2%), ciprofloxacin (78.3%, 90.1%, 87.8%) and cefixime (77.7%, 72.3%, 72.7%).

Conclusions: There was a sharp rise in resistance rates of the S. typhi in Iraq (during 2019–2021) to ceftriaxone and ampicillin, while there were highest sensitivity rates to imipenem, aztreonam and chloramphenicol. The following recommendations were made: (1) Improvement of general hygiene and food safety measures. (2) Emphasis on vaccination and surveillance of Salmonella infection. (3) Rational use of appropriate antibiotics through implementation of treatment guidelines. (5) Educate communities and travelers about the risks of S. typhi and its preventive measures.

KEYWORDS:
Salmonella; typhoid fever; antimicrobial resistance; S. typhi; resistance profile

INTRODUCTION

Salmonella is a genus of rod-shaped (bacillus) Gram-negative bacteria of the family Enterobacteriaceae. It is comprised of two species: *Salmonella bongori* and *S. enterica*. Salmonella species can be classified according to their ability to develop specific pathologies in humans into two main serotype groups: typhoidal and non-typhoidal.[1] Non-typhoidal serotypes (NTS) are zoonotic and can be transferred from animal-to-human and from human-to-human. They usually invade only the gastrointestinal tract and cause salmonellosis while typhoidal serotypes can only be transferred from human-to-human and can cause food-borne infection and bacterial infection of the intestinal tract and occasionally of the bloodstream (which is called typhoid fever) or in addition spreading throughout the body, invading organs and secreting endotoxins (the septic form).[2,3] This can lead to life-threatening hypovolemic shock and septic shock and requires intensive care including antibiotics.[3] According to the World Health Organization (WHO), Salmonella spp. are among the 31 pathogens displaying the highest capability of triggering intestinal or systemic disease in humans among diarrheal and/or invasive agents (viruses, bacteria, protozoa, helminths and chemicals) and the third leading cause of death among food-transmitted diseases.[4] This pathogen was the second leading causative agent of food-transmitted diseases in the European Union and the United States.[4] Globally, infections with *S. typhi* are responsible for approximately 20 million new cases of typhoid each year, and it is one of the most common infections in developing countries and low- or middle-income countries where typhoidal Salmonella is endemic and that have poor sanitation with lack of access to safe food and

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water.5 Infections with *S. typhi* are serious public health problems in Iraq, especially when the antimicrobial resistance of Salmonella species increasing and growing worldwide.[6] The most commonly prescribed antibiotics that are used in the treatment of *Salmonella typhi* are ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, ceftriaxone, cefixime, chloramphenicol fluoroquinolones (ciprofloxacin, ofloxacin, or fleroxacin), azithromycin, Imipenem, aztreonam and tetracycline.[7] Salmonella species are increasingly evolving antimicrobial resistance to several commonly used antimicrobial agents. Historically, the first-line agents (ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole) were the drug of choice for the management of *Salmonella typhi*.[7] However, due to the emergence of multidrug-resistant (MDR) *S. typhi* in the 1970s, fluoroquinolones became the standard of care for the treatment of *Salmonella typhi*.[8] Since the 2000s, there have been frequent reports of decreased ciprofloxacin sensitivity to *S. typhi* in the endemic regions of South and Southeast Asia.[9] Currently, ceftriaxone, a third-generation cephalosporin (intravenous), and azithromycin, a macrolide (oral), are increasingly being used for complicated and uncomplicated typhoid fevers, respectively.[9] However, the indiscriminate use of antibiotics has encouraged resistance and selection for virulent MDR clades; thus, antibiotic resistance in *Salmonella typhi* is now a clinical and economic challenge.[10] In this context, controlling infections caused by Salmonella spp. is a global concern and monitoring its possible contamination routes to humans is essential. The aim of this study was to determine the prevalence and distribution of *S. typhi* infections and its antimicrobial susceptibility pattern among patients in Iraq.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted at the Communicable Diseases Control Center in Iraq (CDCI), where all confirmed cases of *Salmonella typhi* infection occurring in all governorates of Iraq are reported, collected, and documented in this center to be as a database for infection with this disease. The strategy of collection and documentation of *Salmonella typhi* infection cases was done by collecting the patient's information, whether the patient is from primary health care center auditors or outpatient in the consulting clinics, or if the patient is inside one of the hospital's halls (inpatient), the attending physician after diagnoses the *Salmonella typhi* infection with clinical symptoms and confirm it with laboratory investigations, writes the diagnosis of *Salmonella typhi* infection in the communicable diseases register then the health care giver who is responsible for the communicable disease registry will entering data on a daily basis by using special programs and sent it to the Communicable Diseases Control Center to be a database for infection with this disease. In this study, cases of *Salmonella typhi* were collected and sorted over a period of three consecutive years, from 2019 to 2021. The total number of samples entered the study was 1471, comprising 1408 (95.71%) blood samples and 63 (4.28%) stool samples. These samples were distributed across three consecutive years (2019, 2020 and 2021) as follows: 817, 152 and 502, respectively. All demographic and clinical characteristics of patients, comorbidity, type of the samples, epidemiologic information, distribution of Salmonella typhi by age and gender, month-wise distribution of cases in each year and profile of Salmonella typhi resistance and sensitivity to antibiotic were gathered and analysed using the Statistical Package for Social Science (SPSS)- version 16. The result values are presented as numbers and percentages to compare values in all parameters and presented as mean ± standard deviation to estimate the age of patients. The results were presented by using tables. p values ≤ 0.05 were considered significant.

Ethical approval

This study was authorised from Arab Board of Health Specialisations Committee. The permission and approval have also been obtained from Center for Communicable Diseases Control, Public Health Department, Iraqi Ministry of Health.

RESULTS

Distribution and Characteristics of Salmonella typhi in Iraq

The distribution of positive Salmonella typhi in the blood and stool samples in this study is shown in Table I, while the demographic characteristics and clinical manifestations of the patients are shown in Table II.

Age and Gender Distribution of Cases of Salmonella typhi

The distribution cases of *Salmonella typhi* in different age groups showed a varying number of cases in each year of the three consecutive years with significant differences (*p* value ≤0.05), but the age distribution in the three consecutive years reveals the highest rate of cases recorded in age group of young adults between (18–35) years followed by (children ≥ 1 year to18 year) and then middle-aged adults between (36–55) years. In 2019, the highest rate was recorded in age group of young adults between18 and 35 years 325 (39.77%) followed by children ≥ 1 year–18 years 234 (28.64%) and then middle-aged adults between 36 and 55 years 110 (13.46%) while the neonates ≤ one month showed less prevalence of Salmonella typhi 7 (0.85%). In 2020, the highest rate was recorded in the age group of young adults (18–35 years) 82 (53.94%) followed by children ≥ 1 year–18 years 37(24.43%) and then middle-aged adults between 36 and 55 years 18 (11.84%) while the neonates ≤ one month showed less prevalence of Salmonella typhi 3 (1.97%). In 2021, the highest rate was recorded in age group of young adults (18–35 years) 302 (60.16%) followed by children ≥ 1 year to18 years 92 (18.32%) and then middle-aged adults between 36 and 55 years 49(9.76%) while the neonates ≤ one month showed less prevalence of Salmonella typhi 7 (1.39%). In contrast, the distribution of Salmonella typhi cases with the gender the highest rate was recorded in male more than female in all 3 years (2019, 2020, 2021) 464 (56.79%), 89 (58.55%), 302 (60.16%), respectively, with significant difference (p = 0.05) in the distribution of Salmonella typhi cases between male and female in all 3 years as illustrated in Table III.

Month-Wise Distribution of Cases of Salmonella typhi

The epidemiology distribution of cases of Salmonella typhi is also affected by seasonal variations. In the year 2019, we notice that the cases begin to gradually increase until they reach their peak and noticeably in July and June followed by May and August 129 (15.78%), 116 (14.19%), 94 (11.50%) and 71 (8.69%) respectively, and then decreasing gradually

Table I: Frequency and percent of the positive Salmonella typhi in the blood and stool samples, Iraq 2019–2022

	2019	2020	2021	Total
Blood	787 (96.33%)	141(92.76%)	480 (95.62%)	1408 (95.71%)
Stool	30 (3.67%)	11 (7.23%)	22 (4.38 %)	63 (4.28%)
Total	817 (100%)	152 (100%)	502 (100%)	1471 (100%)

Table II: Demographic characteristics and clinical manifestation of patients

Parameters	2019	2020	2021
Age (mean ± SD)	18.75 ± 6.55	17.74 ± 14.18	17.35 ± 12.80
Gender n (%)			
Male	464 (56.79%)	89 (58.55%)	302 (39.84%)
Female	353 (43.21%)	63 (41.44%)	200 (60. 16%)
Comorbidity: n (%)			
Lung infection	88 (10.77%)	18 (11.76%)	87 (17.33%)
Upper respiratory tract infection	98 (11.99%)	22 (14.37%)	73 (14.54%)
Sepsis	60 (7.34%)	8 (5.22%)	76 (15.13%)
Urinary tract infection	110 (13.46%)	43 (28.10%)	68 (13.54%)
Hepatitis	46 (5.63%)	11 (7.19%)	43 (8.56%)
Cardiovascular disease	136 (16.64%)	24 (15.68%)	80 (15.93%)
Hypertension	157 (19.21%0	34 (22.22%)	162 (32.27%)
Malnutrition	43 (5.26%)	11 (7.19%)	23 (4.58%)
Immunocompromised	22 (2.69%)	6 (3.92%)	11 (2.19%)
Systemic lupus erythematosus	10 (1.22%)	1 (0.65%)	0 (0.0%)
Diabetes militias	115 (14.07%)	18 (11.76%)	59 (11.75%)
Clinical manifestation (n) %			
Fever (T>37.2 C)	510 (62.42%)	131 (85.62%)	238 (47.42%)
Nausea	563 (68.91%)	109 (71.24%)	210 (41.83%)
Vomiting	479 (58.62%)	81 (52.94%)	239 (47.60%)
Epigastric pain	382 (46.75%)	63 (41.17%)	211 (42.03%)
Reduced appetite	117 (14.32%)	37 (24.18%)	32 (6.37%)
Myalgia	154 (18.84%)	41 (26.79%)	95 (18.92%)
Headache	515 (63.03%)	103 (67.32%)	320 (63.74%)
Diarrhoea	361 (44.18%)	56 (36.60%)	152 (30.27%)
Constipation	44 (5.38%)	4 (2.61%)	20 (3.98%)
Reduced consciousness	22 (2.69%)	59 (38.56%)	6 (1.19%)

Table III: Age and gender distribution of cases of Salmonella typhi

	2019	2020	2021	P value
Age				
Neonates ≤ 1 month	7 (0.85%)	3 (1.97%)	7 (1.39%)	0.000
Children < 1 year	68 (8.32%)	5 (3.28%)	19 (3.78%)	
Children ≥ 1–18 years	234 (28.64%)	37 (24.43%)	92 (18.32%)	
Young adults (18–35)	325 (39.77%)	82 (53.94%)	302 (60.16%)	
Middle age adults (36–55)	110 (13.46%)	18 (11.84%)	49 (9.76%)	
Older adults (≥55)	73 (8.93%)	7 (4.60%)	33 (6.57%)	
Total	817 (100%)	152 (100%)	502 (100%)	
Gender				
Male	464 (56.79%)	89 (58.55%)	302 (60. 16%)	0.05
Female	353 (43.21%)	63 (41.44%)	200 (39.84%)	
Total	817 (100%)	152 (100%)	502 (100%)	

Table IV: Month-wise distribution of cases of Salmonella typhi

Distribution by months in the years	Salmonella typhi n (%)		
Month	2019	2020	2021
January	60 (7.34%)	34 (22.36%)	46 (9.16%)
February	40 (4.89%)	32 (21.05 %)	26 (5.17%)
March	69 (8.44%)	20 (13.15%)	12 (2,39%)
April	68 (8.32%)	8 (5.26 %)	27 (5.37 %)
May	94 (11.50%)	6 (3.94 %)	14 (2.78 %)
June	116 (14.19%)	10 (6.57%)	96 (19.12%)
July	129 (15.78%)	9 (5.92%)	93 (18.52%)
August	71 (8.69%)	7 (4.60%)	54 (10.75%)
September	49 (5.99%)	7 (4.60 %)	40 (7.96%)
October	38 (4.65%)	6 (3.94 %)	26 (5.17%)
November	20 (2.44%)	7 (4.60%)	37 (7.37%)
December	21 (2.57%)	6 (3.94%)	31 (6.17%)
Total	817	152	502

Table V: Year-wise trend in antibiotic sensitivity and resistance rates of Salmonella typhi in three consecutive years (2019, 2020, 2021)

Antibiotic	Antibiotic resistance and sensitivity rates of Salmonella typhi n (%)					
	2019		2020		2021	
	Resistance	Sensitive	Resistance	Sensitive	Resistance	Sensitive
Ampicillin	630 (77.11%)	187 (22.88%)	117 (76.97%)	35 (23.03 %)	408 (81.27 %)	94 (18.72%)
Ceftriaxone	754 (92.28%)	63 (7.71%)	131 (86.18 %)	21 (13.82%)	446 (88.84 %)	56 (11.15%)
Cefixime	182 (22.27%)	635 (77.72%)	42 (27.63 %)	110 (72.37%)	137 (27.29%)	365 (72.70%)
Chloramphenicol	53 (6.48%)	764 (93.51%)	11 (7.24%)	141 (92.76%)	39 (7.76%)	463 (92.23 %)
Ciprofloxacin	177 (21.66%)	640 (78.33%)	15 (9.87%)	137 (90.13 %)	61 (12.15%)	441 (87.84 %)
Imipenem	29 (3.54%)	785 (96.08%)	5 (3.28 %)	147 (96.71 %)	15 (2.99 %)	487 (97.01%)
Aztreonam	48 (5.87%)	769 (94.12%)	8 (5.26 %)	144 (94.74 %)	21 (4.18 %)	481 (95.82%)
Azithromycin	253 (30.96%)	564 (69.03%)	82 (53.95%)	70 (46.05%)	163 (32.47 %)	339 (67.53 %)
Tetracycline	138 (16.89%)	679 (83.10%)	18 (11.84 %)	134 (88.16 %)	30 (5.98 %)	472 (94.04 %)
Co-trimoxazole	108 (13.21%)	709 (86.78%)	21 (13.82%)	131 (86.18 %)	72 (14.34%)	430 (92.23 %)

until it reaches its lowest number in November 20 (2.44%), also in 2021 the cases reach their peak and noticeably in the of June and July followed by August 96 (19.12%), 93 (18.52%) and 54 (10.75%), respectively, reaches its lowest number in march 12 (2,39%) but in 2020, there is a great disparity and difference in monitoring cases, as it reaches its highest in the first two months of the year January 34 (22.36%) and February 32 (21.05 %) and then begins to decrease to record a few numbers over all the months of the year, In general, it is clear from the results that in Iraq, the peak incidence of *Salmonella typhi* occurs between the months of June, July and August (dry season) as illustrated in Table IV .

The Antimicrobial Susceptibility Pattern of Salmonella typhi

As shown by Table V, there was a dramatic increase in the resistance of *S. typhi* to ceftriaxone (92.28%, 86.18%, 88.84%) and ampicillin (77.11%, 76.97%, 81.27%) in the three consecutive years (2019, 2020, 2021). The highest rates of *Salmonella typhi* resistance to ceftriaxone were in 2019, followed by 2021 and 2020, with close proportions. As for ampicillin, it reached the highest level of resistance to *Salmonella typhi* in 2021, followed by 2019 and then 2020 at similar rates of resistance for both years. Whereas, in the three consecutive years (2019, 2020, 2021) the highest sensitivity rates of *Salmonella typhi* was in imipenem (96.08%, 96.71%, 97.01%), followed by aztreonam in a similar proportion (94.12%, 94.74%, 95.82%) respectively, then followed by chloramphenicol (93.51%, 92.76%, 92.23%) As the top three sensitive antibiotics against *Salmonella typhi*. In the three consecutive years (2019, 2020, 2021), there was noticed and gradual increase in sensitivity of Salmonella typhi bacteria to tetracycline (83.10%, 88.16%, 94.04%) and cotrimoxazole (86.78%, 86.18%, 92.23%) with similar antibiotic sensitivity profile of *Salmonella typhi* for both antibiotic, then followed by ciprofloxacin (78.33%, 90.13%, 87.84%) and cefixime (77.72%, 72.37%, 72.70%). As for azithromycin, there is a decrease in the sensitivity profile to Salmonella typhi, especially in 2020, where it reached less than 50% (46.05%), while it was approaching 70% in 2019 and 2021 (69.03%, 67.53%) respectively.

DISCUSSION

The distribution of *Salmonella typhi* infection cases that were occurring in all governorates of Iraq and reported, documented and collected in the Communicable Diseases Control Center in Iraq (CDCI) showed varying numbers of cases in each 1 year of the three consecutive years (817, 152, 502) in 2019, 2020, 2021, respectively. There was a noticeably decrease in *Salmonella typhi* infection cases in 2020 compared to the other 2 years. A potential several reasons for this decreased rate of infection, such as the start of the COVID-19 pandemic and its subsequent repercussions like restrictions for both public and private gatherings including those where food and drinks are normally served and might provide opportunities for large-scale exposure to *Salmonella typhi* infection, such as receptions, parties, festivals, etc. which reduced the exposure to *Salmonella typhi* infection via contaminated food consumed outside the household moreover reduced exposure to infection due to travelling, people were generally discouraged to travel, the travel restrictions and permitted as only for essential purposes.[11] Our results do not exclude the reasons for reporting compliance when the healthcare system was overwhelmed by COVID-19 cases, and they were giving priority only to severe cases Salmonella typhi infection that requires admission to hospital and recorded them as a result of larger than usual number of *Salmonella typhi* cases with only mild to moderate symptoms that could have been unascertained and unreported in primary healthcare center. Moreover, the patients themselves could have refrained from seeking medical attention (to avoid contagion, reduce burden on

healthcare, etc. Furthermore, increasing personal and household hygiene and continuous sterilisation to reduce the risk of infection with COVID-19 all of them were factors contributing to the decreased the Salmonella typhi infection incidence 2020.[12] The impact of the COVID-19 pandemic on *Salmonella typhi* infection was confirmed with a previous study (Lapo Mughini-Gras et al)[13] that explains the impact of the COVID-19 pandemic on human salmonellosis in the Netherlands. Regarding the monthly distribution of *Salmonella typhi* cases in each year in 2019, it was noted that the incidence of *Salmonella typhi* infection cases was constant with a small increase in the first quarter of the year (January, February, March, April), which begins to increase gradually in the second quarter of the year (May, June, July, August) with its maximum peak in June and July then gradually decreased in September in the third and fourth quarters of the year and continues to decrease significantly throughout the year 2020 at close rate of infection in each month in the year. In 2021, the incidence of *Salmonella typhi* infection had decreased in the first half of the year, until the months of June, July, and August, when the rate of infections started to increase noticeably with its maximum peak in June and July then returned to decreased in the fourth quarters of the year. It is clear from the results that in Iraq, the peak incidence of *Salmonella typhi* occurs between the months of June, July and August (dry season). Regarding the analysis of the distribution of *Salmonella typhi* cases in age groups and gender, it revealed the clustering of cases was recorded in the age group of young adults (18–35 years), and most cases of *Salmonella typhi* were males in all three consecutive tears. The plausible explanation for this age group predominance is the fact that age groups have more outdoor exposure and are more likely to consume street foods as compared to other age groups. Street food consumption is an important risk factor for *Salmonella typhi* which usually results from eating raw or undercooked meat, poultry, eggs, or egg products or drinking unpasteurised milk. Also, reasonable explanation for the male predominance because of the similar reasons that explain young adults (18–35 years) prevalence. The results of this study are in agreement with the previous studies (Umair et al.[14] that conclude the distribution of most of the cases of *S. typhi* belonged to 18–25 years and males. In the analysis of sensitivity and resistance pattern of *Salmonella typhi* to common antimicrobial agents in three consecutive years (2019, 2020, 2021), there was a sharp rise in resistance rates of the *S. typhi* isolates to ceftriaxone and ampicillin, with the highest sensitivity rates of *Salmonella typhi* that were in imipenem followed by aztreonam then followed by chloramphenicol as the top three sensitive antibiotics against *Salmonella typhi* furthermore gradual increase in sensitivity of *Salmonella typhi* to tetracycline and cotrimoxazole with similar antibiotic sensitivity profile for both antibiotics then followed by ciprofloxacin and cefixime but for azithromycin, there is a decrease in the sensitivity profile to Salmonella typhi, especially in 2020 where it reached less than 50%. Although the emergence of antimicrobial resistance is a natural phenomenon, but overprescribing of antibiotics and misuse in humans and animals is accelerating this resistance. The increase in consumption of antibiotics that are easily available over the counter and not clinically justified owing to the lack of any health regulation across the country specially ceftriaxone and ampicillin which are used as first-line treatment for many infections in hospitals and community and overuse of them lead to increase resistance and an important driver of emerging widespread drug-resistant pathogens including *S. typhi*. The frequency and *S. typhi* profiles and their antibiotic sensitivity pattern vary widely from one geographical region to another as well as from one country to country and even center to center or hospital to another. The results of this study were confirmed with the previous reports studies[15] that reported a significantly ceftriaxone-resistant Salmonella typhi outbreak in Pakistan[16] that showed injudicious use of antimicrobials has resulted in the development of antimicrobial resistance among Salmonella pathogens and Salmonella showed widespread resistant to ampicillin which resulted in the use of alternative antimicrobials like fluoroquinolones. The results of this study also confirmed with some results of studies[17] that conclude Salmonella typhi showed the highest sensitivity to imipenem 100 (n = 39) and less sensitivity with ampicillin (14%) and not confirmed with other result of the same study in sensitivity of azithromycin 95%, ceftriaxone 49.4%, cotrimoxazole 33.3%, chloramphenicol 26% and lowest sensitivity was to ciprofloxacin 3.7%.

Our study had a few limitations. First, the data that were taken was during the COVID-19 pandemic and its subsequent repercussions. This may be due to several reasons, including:

- Healthcare strain: The pandemic may have strained healthcare systems, affecting the ability to collect and report Salmonella data.
- Changes in reporting: Shifting priorities during the pandemic could lead to changes in reporting practices, impacting the accuracy and timeliness of Salmonella data.
- Public behaviour changes: Measures like lockdowns and increased hygiene may influence the spread of Salmonella as people change their behaviours.
- Testing challenges: The focus on COVID-19 testing may affect resources for testing other infections, potentially leading to underreporting or delays in identifying Salmonella cases.
- Data Collection Disruptions: Disruptions in routine healthcare services and research during the pandemic may affect the availability and quality of Salmonella-related data.

Secondly, we did not investigate factors responsible for increased resistance. These factors include recent use of antibiotics, over-the-counter use of drugs and the knowledge, attitude and practice of antibiotic prescription and use among healthcare workers and patients. Furthermore, we did not explore the effect of these factors on the prevalence of the burden of *Salmonella typhi*. Additionally, the role of several socio-economic factors, such as sanitation, hygiene, source of water supply and eating habits, was not established in this study. Thirdly, our study did not examine the role of genetic factors in conferring drug resistance to bacterial strains. We suggest conducting frequent studies in the future to keep pace with changes in the prevalence and antimicrobial resistance profile of Salmonella typhi infection in Iraq. Exploring factors contributing to increasing resistance is recommended. This can be achieved through further molecular studies, including genotype studies to detect multidrug resistance in *S. typhi*.

CONCLUSIONS

According to our findings in three consecutive years (2019, 2020, 2021), there was a sharp rise in resistance rates of the *S. typhi* isolates to ceftriaxone and ampicillin, so these antibiotics cannot be used as a potential option for the treatment due to their resistance. There were the highest sensitivity rates to imipenem followed by aztreonam then followed by chloramphenicol as the top three sensitive antibiotics against Salmonella typhi. Other antibiotic like tetracycline, cotrimoxazole, ciprofloxacin, cefixime and azithromycin can also be used, but their use depends on the sensitivity and resistance profile of *Salmonella typhi*. Controlling the prevalence and antimicrobial resistance of *Salmonella typhi* infection involves a multifaceted approach that combines public health measures, healthcare practices and community education. Some recommendations are as follows: 1) water, sanitation, and hygiene (WASH) Improvement, 2)vaccination to reduce the incidence of infection, 3) surveillance and reporting to monitor the prevalence of *Salmonella typhi* infections and detect outbreaks, 4) infection control in healthcare settings to prevent the spread of infection among patients and healthcare workers, 5) rational use of antibiotics through the development and implementation of guidelines for appropriate antibiotic use in the treatment of typhoid fever, 6) educate communities about the risks of *Salmonella typhi* infection and the importance of preventive measures, 7) traveler education about the risks of typhoid fever in endemic areas and recommend preventive measures, including vaccination, 8) food safety measures to prevent contamination of food and water sources, 9) collaborate with international organisations to share best practices, data and strategies for controlling typhoid fever and antimicrobial resistance, 10) invest in research to develop new diagnostic tools, vaccines and treatment options for typhoid fever and 10) advocate for policies that prioritise public health and antimicrobial resistance prevention.

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ORIGINAL ARTICLE

The Development of Gout Treat-To-Target booklet

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ABSTRACT

Introduction: The treat-to-target serum uric acid approach is recommended in local and international guidelines on gout management. Instruction for initiation and dose escalation for urate lowering therapy may cause confusion to the patient. Our aim was to develop and validate Gout Treat-To-Target booklet to aid in patient education.

Materials and methods: A content development team which consisted of three consultant rheumatologists developed the booklet. Content validation was performed by a panel of evaluators consisted of eleven physicians (four consultant rheumatologists, two clinical specialists, and five medical officers), who were involved in gout management. Face validation was performed by ten patients with gout.

Results: Item-Content Validity Index ranged from 0.9 to 1 with regards to relevancy, clarity, ambiguity and simplicity. Side effects of uricosuric agents were added to the draft based on an evaluator's comment. Item-Face Validity Index was 1, which indicated that all patients were in 100% agreement with all items.

Conclusion: We developed and validated our Gout Treat-to-Target booklet. There was high agreement in I-FVI and I-CVI among physicians and patients.

KEYWORDS:
Gout; content validation; Item-Content Validity Index; face validation; Item-Face Validity Index

INTRODUCTION

Gout is a spectrum of disorder ranging from asymptomatic hyperuricemia, acute gouty arthritis, inter-critical gout and advanced tophaceous gout.[1] It is a disabling but treatable disease, and when left untreated, complications such as tophi, urate arthropathy and renal stones ensue.[2,3] Most guidelines recommend starting urate lowering therapy (ULT) when there are two or more episodes of gout flare in a year or when patient develop complications.[1,4,5] Maintaining SUA below the saturation point has been shown to reduce flare frequency and facilitate uric acid crystal dissolutions.[6,7] Therefore, a treat-to-target strategy is recommended where the treatment should target SUA level ≤360 µmol/L in gout without tophi and ≤ 300 µmol/L for gout with tophi.[2] The target SUA should be maintained lifelong if the ULT is well tolerated.[1]

Only a small percentage of patients received ULT, ranging from 29% in United States and 34% in United Kingdom.[8,9] Furthermore, only 10-46% of patients were reported to be adherent to ULT.[10] Inadequate gout education and information from the physicians are among the factors that contribute to non-adherence to therapy.[11-13] Patients perceived gout attacks as an 'inconvenience' which had no negative impact on their overall health, thus they sought solely pain alleviation and dietary management.[14] Patients' belief that gout does not justify long-term treatment and their scepticism over the efficacy of ULT also impede successful gout treatment.[15,16] We conducted this study to develop and validate our Gout Treat-To-Target booklet as a tool to achieve Treat-To-Target strategy.

MATERIALS AND METHODS

The content development, content validation, and face validation of the Gout Treat-to-Target booklet was conducted from April to June 2022. This study was performed in line with the principles of the Declaration of the Helsinki and the approval was granted by Universiti Teknologi MARA Research Ethics Committee [REF: REC/02/2022(FB/12)].

Content development

The content of Gout Treat-to-Target booklet was developed over two months by a team of three consultant rheumatologists with eight to twenty years of experience in gout management. A series of discussions were conducted to review relevant literatures and guidelines (both local and international guidelines). The first draft of the content adapted the Malaysian Clinical Practice Guideline (CPG) for the management of Gout and 2016 updated European Alliance of Associations for Rheumatology (EULAR) evidence-based recommendations for gout management.[17,18] The content developer team also decided on the front page and design of Gout Treat-to-Target booklet. This booklet was written in Malay language to suit to the majority of Malaysian patients who can read and understand Malay. The content of Gout Treat-to-Target booklet are summarized in Table I.

Content validation

The content validation was conducted in May 2022, to assess the relevancy of the items in the booklet. Eleven medical practitioners (four consultant rheumatologists, two clinical specialists, and five medical officers) with experience in gout management were invited to become evaluators and review the content of Gout Treat-to-Target booklet. They rate each item in the booklet from 1 to 4 19, based on:

a) relevancy (1: not relevant, 2: need some revision, 3: need minor revision, and 4: very relevant)

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Table I: The content of Gout Treat-to-Target booklet

Page	Content	Purpose
1	Name, registration number and name of the hospital.	Identification
2	Gout history and complications (tophi, erosion, urate stone) Cardiovascular co-morbidities SUA target	Documentation
3-4	Initiation of allopurinol: Table to document date, SUA, creatinine clearance, dose of allopurinol, and dose of colchicine.	Documentation
5	Initiation of febuxostat: Table to document date, SUA, creatinine clearance, dose of febuxostat, and dose of colchicine.	Documentation
6-10	Continuation of ULT: Table to document date, SUA, creatinine clearance, dose of ULT, and dose of colchicine.	Documentation
11	Appendix A: Gout treatment	Education
12	Appendix B: Information on ULT and colchicine	Education
13	Appendix C: Gout Diet	Education
14	Appendix D: Healthy Lifestyle	Education

Table II: Content Validity ratings by eleven evaluators and Item-Content Validity Index values

Items	Relevancy		Clarity		Ambiguity		Simplicity	
	Panels in agreement, n (%)	Item-Content Validity Index	Panels in agreement n (%)	Item-Content Validity Index	Panels in agreement n (%)	Item-Content Validity Index	Panels in agreement, n (%)	Item-Content Validity Index
Gout								
History	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Comorbidities	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Complications	10 (91)	0.9	11 (100)	1	11 (100)	1	11 (100)	1
Target SUA	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Allopurinol: Treatment initiation								
SUA level	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Creatinine clearance	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Colchicine dose	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Allopurinol dose	10 (91)	0.9	10 (91)	0.9	11 (100)	1	11 (100)	1
Febuxostat: Treatment initiation								
Indication	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
SUA level	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Creatinine clearance	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Dose	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
ULT continuation								
SUA level	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Creatinine clearance	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Dose	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Colchicine dose	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Appendix A: Gout treatment								
Reduce swelling	10 (91)	0.9	11 (100)	1	10 (91)	0.9	11 (100)	1
Urate lowering therapy	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Appendix B: Information on ULT and colchicine								
Allopurinol/Febuxostat	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Benzbromarone/ Probenecid	10 (91)	0.9	10 (91)	0.9	11 (100)	1	11 (100)	1
Colchicine	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Appendix C: Gout diet								
Should be avoided	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Encouraged	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
No restriction	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1
Appendix D: Healthy lifestyle	11 (100)	1	11 (100)	1	11 (100)	1	11 (100)	1

Table III: Face Validity ratings by ten patients and Item Face Validity Index values

Items	Assessment (No of patient in agreement)				
	1 (Not relevant)	2 (Need some revision)	3 (Need minor revision)	4 (Very relevant)	Item Face Validity Index
Gout					
History				10	1
Comorbidities				10	1
Complications				10	1
Target SUA				10	1
Allopurinol: treatment initiation					
SUA level				10	1
Creatinine clearance				10	1
Colchicine dose				10	1
Allopurinol dose				10	1
Febuxostat: treatment initiation					
Indication				10	1
SUA level				10	1
Creatinine clearance				10	1
Dose				10	1
ULT continuation					
SUA level				10	1
Creatinine clearance				10	1
Dose				10	1
Colchicine dose				10	1
Appendix A: Gout treatment					
Reduce swelling				10	1
Urate lowering therapy				10	1
Appendix B: Information on					
ULT and colchicine				10	1
Allopurinol/Febuxostat					
Benzbromarone/ Probenecid				10	1
Colchicine				10	1
Appendix C: Gout diet					
Should be avoided				10	1
Encouraged				10	1
No restriction				10	1
Appendix D: Healthy lifestyle				10	1

b) clarity (1: not clear, 2: need some revision, 3: need minor revision, and 4: very clear)
c) simplicity (1: not simple, 2: need some revision, 3: need minor revision, and 4: simple)
d) ambiguity (1: doubtful, 2: need some revision, 3: need minor revision, 4: no doubt).

Face validation

The face validation was conducted in June 2022, to assess the simplicity and comprehensiveness of each item in the Gout Treat-To-Target booklet. Ten patients with gout were selected via purposive sampling. The patients were asked to give a rating score from 1 to 4 20 based on simplicity and comprehension of each item; (1: the item is not clear and understandable, 2: the item is somewhat clear and understandable, 3: the item is clear and understandable, and 4: the item is very clear and understandable). Rating 1 and 2 represent invalid content or not relevant, while rating 3 and 4 represent valid content or relevance. The patients were also asked to comment on the clarity of the module content, report any the confusing word or sentences, and inform any words that were not acceptable and suggest an alternative word that is commonly used. The comments were taken into consideration to refine the domain and its content to produce the final version of the Gout 'Treat-to-Target' booklet.

Statistical analysis

The qualitative content validity method was employed where the panel of evaluators observed the grammar, the usage of appropriate and correct words, and the application of the correct and proper order of sentences. Content validity was also quantified using Item-Content Validity Index (I-CVI) which was calculated by dividing the number of evaluators that score 3 and 4 for each item by the total number of evaluators. The I-CVI values can range from 0 to 1. With more than five experts, the acceptable value for I-CVI is 0.78. The calculated I-CVI of ≥0.79 indicates relevant items, I-CVI 0.70 to 0.79 indicates items which need revision, and I-CVI of ≤0.70 indicates items which need to be eliminated. The Item Face Validity Index (I-FVI) were obtained by dividing the number of patients that score 3 and 4 for each item by the total number of patients. I-FVI values can range from 0 to 1. Rating 1 and 2 represent invalid content or are not relevant, while ratings 3 and 4 represent valid content or relevance. The value of I-FVI of ≥ 0.79 for each item is considered relevant.

RESULTS

Table II shows the number of evaluators in agreement and I-CVI on each item in the gout Treat-To-Target booklet. More than 90% level of agreement was achieved among the panel of evaluators. I-CVI of all components ranged between 0.9 to

1 with regards to relevancy, clarity, ambiguity and simplicity. Two evaluators suggested to change the word joint 'kerosakan sendi' (damaged joint) to joint erosions and to add side effect for uricosuric agents. The suggestion to add side effects for uricosuric agents were updated to the expert panels and incorporated into the final version of gout Treat-To-Target booklet. In face validity, all patients indicated 100% agreement with all items (I-FVI equal to 1) and the findings are shown in Table III.

DISCUSSION

This study was conducted to develop and validate our Treat-To-Target booklet as a tool to achieve Treat-To-Target strategy in gout management. Other interventions which were shown to be effective in achieving this strategy were nurse-led gout care in general practices, nurse-led rheumatologist-assisted telemedicine intervention and ambulatory care pharmacist-led intervention.[21-23] All these interventions have been shown to aid in gout management in various populations.

We invited eleven physicians to validate the content of Gout Treat-to-Target booklet. There were more than 90% level of agreement achieved among the panel of evaluators with regards to relevancy, clarity, ambiguity and simplicity of the content, and 100% agreement were indicated by all ten patients involved in face validity. The reason for such high agreement is that the booklet only include the most important aspects of gout management, which were expressed in short sentences. Apart from avoiding the use of long sentences, figures and diagrams were used instead. Layman's terms were used as much as possible.

Local and international guidelines recommend allopurinol as the first-line ULT.[4,24] It should be started at a lower dose and up-titrated according to SUA levels. The up-titration can be confusing and can result in patients taking the wrong dose of medications. In pages of three to ten of Gout Treat-to-Target booklet contains tables which allows physicians to document the dose of ULT and the specific dates for ULT up-titration, as well as the SUA and creatinine clearance. Thus, patients can always refer to the booklet.

Limited gout knowledge among patients is an important barrier to successful gout treatment. Patients were not aware of the potentially progressive features of the disease such as tophi development and joint damage, the fact that gout could be controlled with medications to lower SUA, and the paradoxical gout attacks can occur with ULT initiation, which resulted in patients subsequently stopped taking their ULT.[25] Personal health literacy, according to Healthy People 2030, is defined as the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.[26] Gout Treat-to-Target booklet contains information on gout medications, diet restrictions and suggested lifestyle, which would allow patients to understand and inform their decisions to the physicians. It is a tool which can be used in clinical practice to empower patient's health literacy in gout.

Physician factor is the other important barriers of successful gout treatment. Many were not aware of or did not follow gout management guidelines. Although allopurinol was the most commonly prescribed ULT, the starting dose ranged 50 mg to 300 mg. Only half of the physicians reported up-titrating allopurinol, and some non-rheumatologists were hesitant to exceed allopurinol dose of 300 mg.[25] Booklets had been used as education tools not only for patients but also for healthcare providers. An example is a patient-education booklet which was created to overcome identified barriers to the delivery of recommended care. The booklet reminded the professionals of the guidelines and made it easier to follow them.[27] Similarly, Gout Treat-to-Target booklet can serve as a guide for non-rheumatologists during consultation with patients to ensure that to the key points in gout management are relayed.

One of the limitations of our study was that Gout Booklet is only available in Malay. Our reason for doing this was because most Malaysians, regardless of their ethnicities are well-versed in Malay language. Moving forward, future study should include translating Gout Treat-to-Target booklet to other languages, so that it can be used for other ethnicities locally and internationally. A study should be conducted to investigate the effectiveness of Gout Treat-to-Target booklet in clinical practice. Lastly, in the era of digital and technology, Gout Treat-to-Target booklet should be developed as online application.

CONCLUSION

The Gout Treat-to-Target booklet had been successfully developed. We conducted content and face validity, with very good agreement among the evaluators and patients, respectively.

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The roles of ceramides and multivesicular emulsion (MVE) technology in atopic dermatitis: a narrative review

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a highly prevalent chronic inflammatory skin condition. In Malaysia, a prevalence of 13.4% was reported for children between one and six years of age, one of the highest prevalence rates of AD in Asia. Many guidelines recommended moisturisers as the mainstay of treatment strategy for AD. Selecting an effective and suitable moisturiser for people with AD plays a crucial role in avoiding acute exacerbation of AD and achieving remission.

Materials and Methods: Given that an array of active ingredients and topical vehicles for moisturisers are available in the market, this review summarised the roles of ceramides and multivesicular emulsion (MVE) technology in managing AD to help guide treatment decisions.

Results: Ceramides are essential in maintaining the skin permeability barrier and hydration, modulating skin immunity through anti-inflammatory and antimicrobial defence system, and regulating cellular functions. Low levels and altered structures and composition of ceramides, compromised skin permeability barrier and increased trans-epidermal water loss were commonly observed in AD patients. Most clinical studies have shown that ceramide-dominant moisturisers are safe and effective in adults and children with AD. MVE technology offers an attractive delivery system to replenish ceramides in the SC, repairing the compromised skin permeability barrier and potentially improving patient compliance.

Conclusion: Recommending clinically proven therapeutic moisturisers with the right ingredients (level, ratio, structure and composition), alongside an effective sustained release delivery system, to AD patients is one key strategy to successful disease control and flare prevention, subsequently reducing the disease burden to patients, families and societies.

KEYWORDS:
Ceramide; multivesicular emulsion; atopic dermatitis; eczema; moisturisers

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a highly prevalent chronic inflammatory skin condition. In Asia, the AD prevalence varies with countries, ranging from 4.3 to 19.6% in children and 1 to 4.6% in adults. In Malaysia, a prevalence of 13.4% was reported for children aged between one and six years, one of the highest prevalence rates of AD in Asia.[1] AD is characterised by intense itching, dry skin and inflammation. AD follows a relapse-remitting course, with periods of acute worsening ('flares') alternating with relative quiescence after proper treatment.[2]

While AD has long been attributed to immunological abnormalities, it is now recognised that a defective skin permeability barrier is one key driver of disease activity in AD (i.e., barrier-initiated pathogenesis of AD). Firstly, disruption of the skin permeability barrier alone directly stimulates the production of proinflammatory cytokines (e.g. IL-1b, IL-6 and IL-8) in the epidermis as a repair response, triggering skin inflammation and producing AD symptoms.[3-5] Besides that, the genes encoding skin barrier structural components (filaggrin and loricin) are expressed in response to the impaired skin permeability barrier, leading to excessive inflammation and tissue hyperplasia. Impaired skin permeability barrier also increases trans-epidermal water loss (TEWL) and reduces skin hydration, further stimulating the release of proinflammatory cytokines and compromising the skin permeability barrier function. Lastly, as the skin permeability barrier forms a protective layer against exogenous substances, skin permeability barrier dysfunction increases the risk of pathogen colonisation, particularly Staphylococcus aureus[6], resulting in infections and subsequent IL-17 and IL-22-mediated inflammation.[3,4,6] Therefore, maintaining an effective and functional skin permeability barrier is essential to prevent acute exacerbation of AD and achieve disease remission.

Stratum corneum (SC), the outermost layer of the skin, develops before birth and becomes visible at 34-week gestational age. After birth, SC maturity continues up to about 4 years of age.[7,8] SC is composed of two distinct compartments: hydrophilic corneocytes (dead and terminally differentiated keratinocytes) and extracellular hydrophobic lipid matrix (lipid lamellae). The lipid lamellae are composed of ceramides (~50%), cholesterol (~25%), and free fatty acids (~15%), with smaller quantities of phospholipids and cholesterol sulphate. These hydrophobic lipids are tightly packed and arranged in multiple bilayers (lamellae) within the extracellular domains of the SC to prevent TEWL and invasion of environmental irritants, pathogens, and allergens.[5,9] The corneocytes, which are composed of filaggrin and a collection of water binding molecules known as natural moisturising factor (NMF), absorb water from epidermis to SC and prevent TEWL from SC to keep the skin

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Table I: The main types of ceramides in human SC

Fatty acid / Sphingoid	Non-hydroxy fatty acid (N)	α-hydroxy fatty acid (A)	Esterified ∞-hydroxy fatty acid (EO)
Dihydrosphingosine (DS)	CER (NDS) Ceramide 10	CER (ADS) Ceramide 11	CER (EODS) Ceramide 12
Sphingosine (S)	CER (NS) Ceramide 2	CER (AS) Ceramide 5	CER (EOS) Ceramide 1
Phytosphingosine (P)	CER (NP) Ceramide 3	CER (AP) Ceramide 6	CER (EOP) Ceramide 9
6-hydroxy sphingosine (H)	CER (NH) Ceramide 8	CER (AH) Ceramide 7	CER (EOH) Ceramide 4

hydrated.[4] These corneocytes are held in place by a highly cross-linked protein structure called cornified envelope (CE), which binds covalently with a monolayer of insoluble lipids, mainly ceramides, forming the cornified lipid envelope (CLE). The CLE works like a scaffold, supporting the corneocytes within extracellular lipid lamellae and plays an important role in maintaining the skin permeability barrier function.[5,9]

Infant skin differs from adult skin at the microstructural, functional and compositional levels, and these differences lead to different water-holding properties and clinically observed differences between infant and adult skin.[8] In infants, the SC is thinner. Despite higher SC hydration in infants compared with adults, infant TEWL is significantly higher than adults and the levels of NMF and lipid components are significantly lower in infants up to 1 years of age.[7,10] These parameters change rapidly over the 1st year of life and are stabilised towards adult values by 3–5 years of age.[8] These developmental changes impacted the skin permeability barrier in children, resulting in a more sensitive and permeable skin that is susceptible to irritation and inflammation.[10] The age-dependent changes in children skin permeability barrier, which are believed to be fully matured to adult values by approximately 5 years of age, explained the higher prevalence of AD amongst children relative to adults.[8,10]

Due to robust clinical evidence demonstrating that regular use of moisturisers reduces the severity of AD, prolongs the time to next flare, and reduces the need for rescue topical corticosteroid (TCS),[11] many guidelines including American Academy of Dermatology (AAD),[2] and Malaysia Clinical Practice Guideline[12] recommended moisturisers as the mainstay of treatment strategy. Moisturisers increase skin hydration and ameliorate skin dryness by exerting humectant, occlusive, and emollient effect. While humectants (e.g., glycerine, hyaluronic acid, urea) mimic the NMF in corneocytes to attract and bind water from deeper epidermis to SC, occlusives (e.g., lanolin, mineral oil, olive oil, petrolatum) act like the intercellular lipid bilayers to form a hydrophobic film and slow down TEWL from the SC whereas emollients (e.g., collagen, colloidal oatmeal, shea butter, glyceryl stearate, isopropyl palmitate, stearic acid) function like natural lipids on the SC, filling the cracks between the corneocytes and smoothening the skin.[13]

Various topical vehicles and formulation technologies were designed to sustainably deliver active ingredients to the targeted skin site at an appropriate level. Common vehicles included chemical penetration enhancers (e.g., propylene glycol, oleic acid, isopropyl myristate, ethanol) or physical occlusives (e.g., lipids and hydrocarbons ointment). Physical occlusives increase the skin hydration and markedly increase skin penetration of applied ingredients. Chemical penetration enhancers facilitate both the partitioning into and the passage of ingredients through the skin. Besides physical occlusives and chemical penetration enhancers, other formulation technologies such as liposomes, noisomes, nanoparticles, transferosomes, ethosomes, and multi-vesicular emulsions (MVE) were introduced to enhance the delivery of active ingredients to the skins. Given that selecting an effective and suitable moisturiser with the right active ingredients and topical vehicles at the right levels plays a crucial role for people with AD in achieving remission and avoiding acute exacerbation of AD, this study aims to review the roles of ceramides and the latest multivesicular emulsion technology in managing AD.

THE ROLES OF CERAMIDES IN ATOPIC DERMATITIS

Ceramide comprises fatty acids (FA) and sphingosine bases (SB) (Fig. 1).[5] Ceramides are classified by a combination of the abbreviations of FA and SB (Table I).[5,14]

There are five types of FAs in human SC: non-hydroxy (N), α-hydroxy (A), esterified ω-hydroxy (EO), ω-hydroxy (O), and β-hydroxy (B), each contributing to 59.4%, 32.5% 6.3%, 1.6%, 0.17% of the human ceramides, respectively.[14] While there are five types of SBs in human SC: dihydrosphingosine (DS), sphingosine, (S) phytosphingosine (P), 6-hydroxy sphingosine (H), and 4,14-sphingadiene (SD), SD-type ceramide is present in small amount in human SC (0.4%). In the human SC, the most abundant ceramides were Ceramide 3, Ceramide 8, and Ceramide 7 (24.2%, 23.7%, and 18.0% of total ceramides, respectively), followed by Ceramide 6, Ceramide 10, Ceramide 2, Ceramide 5, Ceramide 4, Ceramide 1, Ceramide 9 and Ceramide 11 (in descending order, 1 to 9%). Other ceramide classes constitute lower than 1% of human SC.[14]

Many studies consistently found that the total ceramide levels were markedly reduced in patients with AD compared with those with healthy skin, suggesting that low levels of ceramides in the SC impaired the skin permeability barrier, allowing irritants and allergens to permeate the skin, initiating the inflammatory process of AD.[15] Specifically, Ceramide 1 and 3 levels were significantly lower in AD patients than in healthy skin.[12,15] Ichikawa et al.[15], who used a more precise liquid chromatography-mass spectrometry, observed that the levels of Ceramide 4, Ceramide 8 and

Table II: Summary of clinical evidence for ceramide-dominant moisturisers

Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Gupta et al. (2023)[20]	RCT (double-blind, vehicle-controlled)	Children (<18 years)	Aqua Oat Moisturizing Cream vs. Olesoft Max Cream (paraffin-based cream)	- The mean change in SCORAD at 3 months in the ceramide-based and paraffin-based moisturizer groups was 22.1 and 21.4, respectively (p = 0.37). - The change in CDLQI/IDLQI, TEWL over forearm and back, amount and days of topical corticosteroid required, median time to remission and disease-free days at 3 months were similar in both groups. - Both the paraffin-based and ceramide-based moisturizers were comparable.
Na et al. (2010)[21]	Cohort study	Children (aged 5 to 19 years)	Atobarrier cream (no comparator)	- The SCORAD value decreased dramatically after 4 weeks of moisturizer application (p = 0.000). - The TEWL was not changed, but the SC hydration increased significantly (p = 0.000). No significant adverse effects were observed. - Moisturizer containing lipid granules effectively controlled atopic dermatitis.
Danby et al. (2016)[22]	Cohort study	Adults (aged ≥ 60 years)	Balneum cream vs. Aquamol cream	- Treatment with the test emollient for 28 days significantly reduced TEWL and skin surface pH by an average of 1.07 ± 0.29 g/m2/h and 0.15 ± 0.07 pH units compared to the untreated control site, respectively. - Hydration was increased significantly (+2.09 ± 0.95 units) compared to the untreated control despite the last application being ≥12 h previously. - Neither treatment adversely affected lipid chain conformation.
Koh et al. (2017)[23]	Cohort study	Children (aged 6 months to 6 years)	Ceradan Cream (no comparator)	- The mean change in SCORAD and PEST scores from baseline to week 12 was -11.46 (p<0.0001) and -1.33 (p<0.0001) respectively. - The ceramide-dominant therapeutic moisturizer used was safe and effective in the management of AD in young children.
Shindo et al. (2022)[24]	RCT (double-blind, vehicle-controlled)	Adults (23–64 years old)	Ceramide-care Cream vs. water in oil type emulsion	- Both moisturizers improved the visually evaluated skin symptoms and skin hydration. - No statistically significant difference in skin hydration and TEWL between treatment and control arms at week 4. - Moisturizer containing pseudo-ceramide and the eucalyptus extract significantly improved cutaneous barrier function and significantly increased the ceramide level in the stratum corneum
Draelos et al. (2008)[25]	RCT (investigator-blind)	Children and adult (aged 5 to 80 years)	CeraVe Hydrating Cream/Cleanser + fluocinonide cream vs. CeraVe Hydrating cleanser + fluocinonide cream vs. bar cleanser + fluocinonide cream	- The incidence of clearing at week 4 increased from 15% (fluocinonide cream 0.05%+ bar cleanser) to 76% (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser + moisturizing cream) with P=0.0001, and to 37% (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser) with P=0.0001. - The time to clearing was 3.0 weeks in treatment group 3 (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser and moisturizing cream), 3.4 weeks in treatment group 2 (fluocinonide cream 0.05% + MVE ceramide-containing liquid cleanser), and 3.7 weeks in treatment group 1 (fluocinonide cream 0.05% + bar cleanser). - For all signs and symptoms, treatment group 3 experienced the fastest onset and greatest improvement at all time points, followed by treatment group 2 and treatment group 1. - No adverse events and tolerability issues reported by either the investigator or the subjects.
Lynde et al. (2014)[26]	Cohort study	Adult and Children (aged 2 to 88 years)	CeraVe Hydrating Cream (no comparator)	- At day 42, SCORAD scores for group 1 (≥12 years old) and group 2 (<12 years old) showed significant improvement (P=0.0001). - No adverse effects were reported during the 6-week of evaluation. - Ceramide-containing cleanser and moisturiser regimen substantially improved skin condition and clinical outcomes related to AD severity as well as QOL aspects.
Danby et al. (2020)[27]	RCT (double-blind, intrapatient- and vehicle-controlled)	Adult (aged ≥ 18 years)	CeraVe Hydrating Cream/Lotion vs. Zerobase/Epimax/Aquamax Cream	- The test cream and lotion both significantly increased skin hydration and reduced skin dryness for at least 24 hours following a single application compared to a no treatment control site. - Compared to three reference emollient creams the test cream and test lotion were the only products capable of sustaining clinically meaningful improvements in skin moisturiza- tion for 24 hours. - The sustained moisturization imparted by the test products reduces the need for frequent emollient application, often requiring 3–4 applications per day for tradi- tional emollients, and should reduce the high burden of managing dry skin conditions like AD.
Danby et al. (2022)[28]	RCT (observer-blind, intrapatient- and vehicle-controlled)	Adult (aged ≥ 18 years)	CeraVe Hydrating Cream vs Zerobase cream (paraffin-based cream)	Skin barrier integrity was greater at sites treated with the test cream (effect size for area under the transepidermal water loss curve -162, p< 0.0001). Skin sensitivity to sodium lauryl sulfate was reduced (-5 points visual redness, p< 0.0001), as was transepidermal water loss (-15.3 g/m2h, p< 0.0001) compared with the reference. - Sites treated with the test cream displayed enhanced lipid chain ordering, which was significantly associated with skin barrier integrity (r = 0.61). Compared with the reference, treatment with the test cream increased hydration (8.61 capacitance units, p< 0.0001) and decreased signs of dryness.

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Table II: Summary of clinical evidence for ceramide-dominant moisturisers

Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Hon et al. (2013) [29]	Cohort study	Children (aged < 18 years)	Cetaphil Restoraderm Skin Restoring Lotion (no comparator)	- Two thirds of the patients reported very good or good acceptability of the LMF moisturizer, whereas one third reported fair or poor acceptability. - The objective SCORAD score, pruritus score, and sleep disturbance score were lower in the very good/good acceptability group than in the fair/poor acceptability group. - The mean objective SCORAD score improved (from 31.5 to 25.7; p = 0.039) and skin hydration improved from 30.7 to 36.0 (p = 0.021) in the very good/good acceptability group.
Simpson et al. (2013) [30]	RCT (investigator-blinded, intrapatient-controlled)	Adults (aged 18 to 65 years)	Cetaphil Restoraderm Moisturizer vs. no treatment	- After 4 weeks of treatment, significantly greater reduction of TEWL and clinical dryness scores, and increased skin hydration (all p < 01) in the CRM-treated than untreated area. - A significantly higher level of ceramide (p < 05) and a trend toward increased water content was observed in the SC for CRM than for the control. - There were no related AEs.
Ma et al. (2017) [31]	RCT (investigator-blinded, parallel-group, controlled study)	Children (aged 2 to 12 years)	Cetaphil Restoraderm Skin-restoring moisturizer and cleanser vs. no moisturiser and cleanser only	- A significantly earlier onset of action in terms of fewer flares favoring moisturizer was found at week 4 (31 vs. 59%, respectively, p = 0.022), and after 12 weeks, fewer flares occurred (50 vs. 72%). - At week 12 for flare-free subjects, nearly half in both groups had clear IGA, and an emollient effect in terms of less dryness or burning was more marked for moisturizer/body wash. - Both products led to high patient satisfaction and were well tolerated. - A regimen incorporating a moisturizer plus body wash delayed AD flares by nearly 2 months compared to body wash alone, and yielded high patient satisfaction.
Leshem et al. (2020) [32]	RCT (observer-blind, intrapatient- and vehicle-controlled)	Children and adults (aged ≥ 12 years)	Cetaphil Cream vs Aveeno Moisturizing Cream vs CeraVe Moisturizing Cream vs Vaseline	- Mean TEWL improved in the treated forearm and worsened in the untreated one, but the difference was not significant. - There was no significant change in pH or in TEWL after tape stripping. - Capacitance significantly improved in the moisturizer forearm. - The effects of moisturizers on nonlesional AD skin were small and need to be addressed when powering future studies.
Hon et al. (2011) [33]	Cohort study	Children (aged 5 to 18 years)	Curel Moisture Cream (no comparator)	- Four weeks following the use of the cream, skin hydration improved significantly and fewer patients were using topical corticosteroids. - There was no deterioration in transepidermal water loss, eczema severity, or quality of life.
Seghers et al. (2014) [34]	Cohort study	Children and adults (aged 7 to 60 years)	Curel Moisture Cream (no comparator)	- The objective scoring atopic dermatitis decreased from 29.1 at week 0 to 22.0 at week 4 (p < 0.001). - There was no detectable difference in TEWL after 4 weeks. - However, SC hydration was significantly increased from 39.7 at week 0 to 49.2 after 4weeks (p < 0.001). - Both Dermatology Life Quality Index and patient-oriented eczema measure showed significant improvement at week 4 (p < 0.001). - The moisturizer was well tolerated with no serious adverse events recorded.
Mori et al. (2018) [35]	RCT (single-blind)	Female with mild AD (≥ 18 years)	Curel Moisture Gel Lotion vs. no treatment	- Skin dryness and scaling significantly improved with or without application of the moisturising gel. - However, the improvement in dryness of the treated group was significantly higher than that of the nontreated group. - Erythema and itchiness were significantly improved only in the treated group. - The skin hydration on the forearm increased significantly only in the treated group. - Accompanying those improvements, the quality of life of the subjects, evaluated by Skindex-16®, was significantly improved.
Koppes et al. (2016) [36]	RCT (double-blind, vehicle-controlled)	Adults (aged ≥ 18 years)	Dermalex Eczema Cream (Cer-Mg) vs. hydrocortisone acetate cream 1% vs. unguentum leniens (cold cream)	- After 6 weeks, group I (Cer-Mg + Hydrocortisone) showed comparable significant improvement in SCORAD and TEWL between Cer-Mg sites and Hydrocortisone sites, while in group II (Cer-Mg + emollient), the decrease in SCORAD and TEWL was significantly greater at Cer-Mg sites compared with emollient-sites. - Cer-Mg cream was more effective in improving skin hydration and maintenance of levels of NMF than hydrocortisone and emollient.
Sugarman et al. (2009) [37]	RCT (investigator-blinded, vehicle-controlled)	Children (unspecified)	EpiCeram Skin Barrier Emulsion vs. Cutivate cream (fluticasone)	- EpiCeram reduced clinical disease severity, decreased pruritus and improved sleep habits both 14 and 28 days after initiation of therapy. - Although the fluticasone-treated group showed significantly greater improvement at 14 days, SCORAD, pruritus and sleep habit scores for EpiCeram did not differ significantly from the fluticasone-treated group by 28 days.
Kircik et al. (2011) [38]	Cohort study	Children and adults (all ages)	EpiCeram Skin Barrier Emulsion (no comparator)	- Approximately half of the subjects achieved success with investigator global assessment (clear or almost clear scores) after 3 weeks of treatment with test cream monotherapy or in combination with another treatment. - A large proportion of subjects (75%) and investigators (77%) reported satisfaction after three weeks of treatment. Pruritus and quality of life improved during the study.

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Table II: Summary of clinical evidence for ceramide-dominant moisturisers

Author, Year	Type of study	Study population	Intervention vs Comparator	Study outcomes
Miller et al. (2011)[39]	RCT	Children (aged 2 to 17 years)	EpiCream vs. Atopiclair (Glycyrrhetinic-acid containing barrier repair cream) vs. Eucerin cream (petroleum-based skin protectant moisturizer)	- All three groups showed improvement in Investigator's Global Assessment (IGA), the Petroleum-based group was the only group to demonstrate statistically significant improvement in all assessments, including IGA, Eczema Area and Severity Index (EASI), visual analog scale (VAS) for itch intensity, and body surface area (BSA) involvement by day 21 (P <0.05). - No statistically significant difference for any clinical efficacy assessment was found between the three groups at each time point. - However, Petroleum-based cream was found to be at least 47 times more cost-effective than Glycyrrhetinic aicd- or Ceramide-based cream.
Weber et al. (2015)[40]	RCT	Children (aged 3 months to 12 years)	Eucerin Eczema Relief Body cream (maintenance) and Eczema Relief Instant Therapy (acture flare) vs. no treatment	- The incidence of flare was significantly lower in the moisturizer group compared with the control group (21% vs 65%; P=0.006), while the median time to flare was shorter in the control group (28 vs >180 days). - Risk of flare was reduced by 44.1% after 6 months of Body Cream application. - Flare Treatment reduced overall eczema symptom severity at week 2 and week 4; 78.9% of flares had improved or cleared at week 4.
Ishida et al. (2011)[41]	Cohort study	Adults (aged 29 to 71 years)	Extemporaneous preparation with psuedoceramide (no comparator)	- Four weeks of treatment with pseudoceramide cream significantly reduced skin symptoms, accompanied by significant decreases in transepidermal water loss and increases in water content. - TEWL values decreased significantly at week 2 and 4 during the 4 weeks of treatment with the psuedoceramide lotion and remained at a lower level at day 3 in the regression phase in the AD lesional skin. - The level of pseudoceramide that penetrated into the SC was significantly correlated with the SC water content but not with transepidermal water loss.
Draelos et al. (2018)[42]	Cohort study	Children and adults (aged 1 to 86 years)	NeoCera cream (no comparator)	- Use of the ceramide cream resulted in a 100% improvement in IGA scores and a 67% improvement in overall subject skin assessment scores after 4 weeks of treatment and the improvements were statistically significant. - Statistically significant improvements were also observed in transepidermal water loss, water content of the skin, and skin smoothness. - Adverse events were not observed.
Spada et al. (2021)[43]	RCT (double-blind, placebo-controlled)	Adults (aged ≥ 18 years)	QV Intensive Cream vs. placebo cream	- Eczema area severity index score decreased significantly across all time points in both groups compared to baseline (P < .0001), however, this decrease was not significant between groups at day 28 (P = .7804). - In contrast, TEWL and skin hydration significantly improved over time in the active group, while it either stayed the same or worsened in the placebo group (P = 0.0342 and P < 0.0001, respectively). - There was no difference in the use of mometasone furoate as rescue medication over time between groups (P = .1579). - Dermatology life quality index scores improved significantly in both groups (P <0 .0001), with no difference between groups (P = 0.5256). - However, patient satisfaction was greater in the active compared to the placebo group for several parameters including relief of itch, dry skin, skin softness and smoothness (all P < 0.05). - No patients withdrew from the study due to adverse events (AEs) and there were no serious AEs.
Berardesca et al. (2002)[44]	RCT	Children and adults (unspecified)	Repositol vs. Alfason Repair vs. Locobase Repair vs. Nouriva Repair	- Both treatment groups statistically improved all parameters considered at week 4 and 8 as compared to baseline. - Between the 2 treatment groups, there was a statistically significant difference in favour of combined therapy: erythema, pruritus and overall disease severity; erythema and pruritus; erythema, pruritus, fissuring and overall disease severity. - No statistically significant difference was found for: dryness, scaling and fissuring; scaling, fissuring and overall disease severity; dryness and scaling.
Chamlin et al. (2002)[45]	Cohort study	Children (aged ≤ 12 years) with stubborn-to-recalcitrant AD	Tricream (no comparator)	- SCORAD values improved significantly in 22 of 24 patients by 3 weeks, with further progressive improvement in all patients between 6 and 20 or 21 weeks. - TEWL, which were elevated over involved and uninvolved areas at entry, decreased in parallel with SCORAD scores and continued to decline even after SCORAD scores plateaued. - Both SC integrity (cohesion) and hydration also improved slowly but significantly during therapy. - Finally, the ultrastructure of the SC, treated with ceramide-dominant emollient, revealed extracellular lamellar membranes, which were largely absent in baseline SC samples.

Table III: Recent advances in topical formulation technology over the years

Year	Formulations	Components	Mechanism of actions/functions
1964	Liposomes [47]	Self-assembled (phospho)lipid-based drug vesicles that form a bilayer (unilamellar) and/or a concentric series of multiple bilayers (multilamellar) enclosing a central aqueous compartment.	• protect the encapsulated active ingredients from physiological degradation • control the release of active ingredients • extend the half-life of the active ingredients • selectively deliver the active ingredients to the targeted site, thus decreasing the systemic side-effect, elevating the maximum-tolerated dose, and improving therapeutic benefits
1970s	Noisomes [48]	Self-assembled vesicles from non-ionic surfactants with cholesterol that forms lamellar structures	• act as a depot, releasing the drug in a controlled manner • delay clearance from circulation and protect the entrapped active ingredients from the biological environment • enhance the bioavailability of active ingredients and restrict their effects to target cells
1990s	Nanoparticles [49]	Lipid molecules with particle size on the nano- to sub-micron scale (50–1000 nm) after active ingredients encapsulation and are composed of biocompatible and biodegradable components which do not require the use of organic solvents for their assembly	• improve intracellular permeation and increase bioavailability of active ingredients • allow efficient delivery and control release of active ingredients to the targeted sites
1991	Transferosomes [50]	Ultradeformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core	• able to reach intact deeper regions of the skin after topical administration, delivering higher concentrations of active substances and making them a successful drug delivery carrier for transdermal applications
1997	Ethosomes [51]	Soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water	• enable active ingredients to reach the deep skin layers and / or the systemic circulation as ethanol is an efficient permeation enhancer
2004	Multivesicular emulsion (MVE)[52]	Concentric layers of oil-in-water emulsions where one vesicle is contained within another inside the MVE.	• enhance the effectiveness of individual ingredients used on the skin, with time-released or sequential delivery after initial application

Ceramide 9 were also significantly reduced in AD patients on top of the Ceramide 1 and Ceramide 3 levels that have been previously reported. In contrast, the level of Ceramide 5 was elevated in AD patients. Most importantly, this study found that low levels of all ceramides (except Ceramide 2, 5 and 11) increased TEWL and reduced skin hydration, while all ceramide levels (except Ceramide 2 and 5) correlated with skin permeability barrier function. Notably, Ceramide 2 has a unique contribution to AD. While the short-carbon-chain Ceramide 2 was commonly found in AD patients, the long-carbon-chain Ceramide 2 level was reduced in AD patients, suggesting that the structures of ceramides affect the skin permeability barrier.[15] A more recent Japanese study reported a significant difference in Ceramide 6 between AD non-lesional and lesional skins, and between non-lesional and normal skins,[16] providing more granularity to the importance of maintaining the level of Ceramide 6 in AD skins.

Besides the right level and structure of ceramide, the composition of ceramide is important in maintaining the permeability barrier functions. Unique changes in ceramide composition were observed in AD patients. AD patients had significantly lower ratios of several ceramide subclasses (Ceramide 3:2, Ceramide 8:2, Ceramide 3:5, Ceramide 8:5, Ceramide 10:5, Ceramide 7:5, Ceramide 9:5) compared to healthy patients.[5,14] The changes in ceramide composition disrupted the structure of the lipid lamellae and the corneocyte lipid envelope, impaired the functionality of the skin permeability barrier, increased TEWL and reduced skin hydration.[5,14]

While most moisturisers reduce cytokine production by improving skin permeability and restoring SC hydration, ceramides and their metabolites (sphingoid base, sphingosine-1-phosphate and ceramide-1-phosphate) also modulate skin immunity. Firstly, the FA and sphingosine exhibit potent activity against bacterial, yeast, and viral pathogens, and such inhibition of pathogen colonisation reduce superantigen-initiated inflammation.[3,6] Secondly, the ceramide metabolites stimulate innate immunity by increasing the synthesis of antimicrobial peptides in response to external stress, such as ultraviolet irradiation and other types of oxidative stress, protecting the skin against external stressors in the absence of microbial infection.[17] Thirdly, ceramide metabolites activate two acidic pH-dependent enzymes, which increase the production of ceramides required to form the extracellular lamellar bilayers. Lastly, ceramide metabolites inactivate kallikreins, which are activated at high pH skin of AD patients to disrupt the SC integrity.[18] The critical role of ceramides in the anti-inflammatory pathway explained the reason behind altered ceramides levels and compositions commonly observed in lesional skin compared to non-lesional skin.[15]

Apart from forming the basis of SC's physical and chemical defence system, ceramides and their metabolites regulate cellular functions, including cell cycle arrest, differentiation and apoptosis. They add anti-mitotic and pro-cell death features to cells, including in keratinocytes,[17] potentially reducing the risk of skin lichenification in patients with persistent AD. Upon topical application, ceramides not only

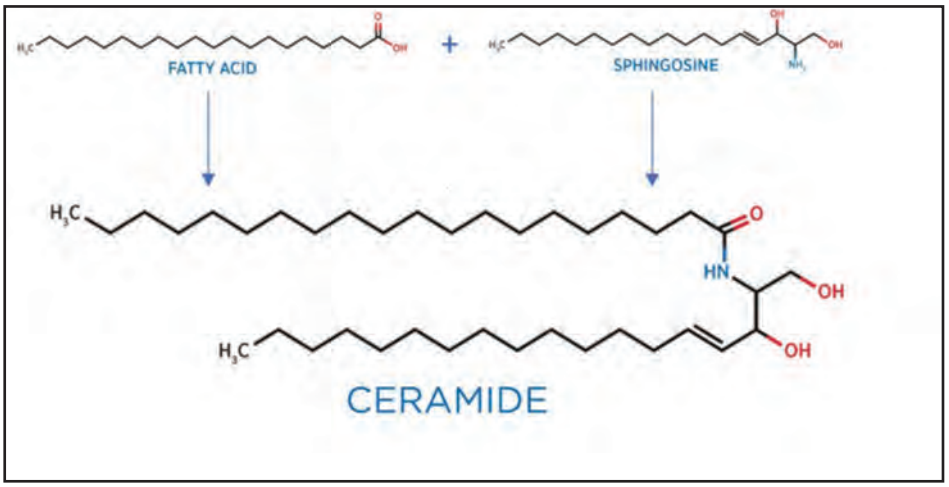

Fig. 1: Ceramide composition.

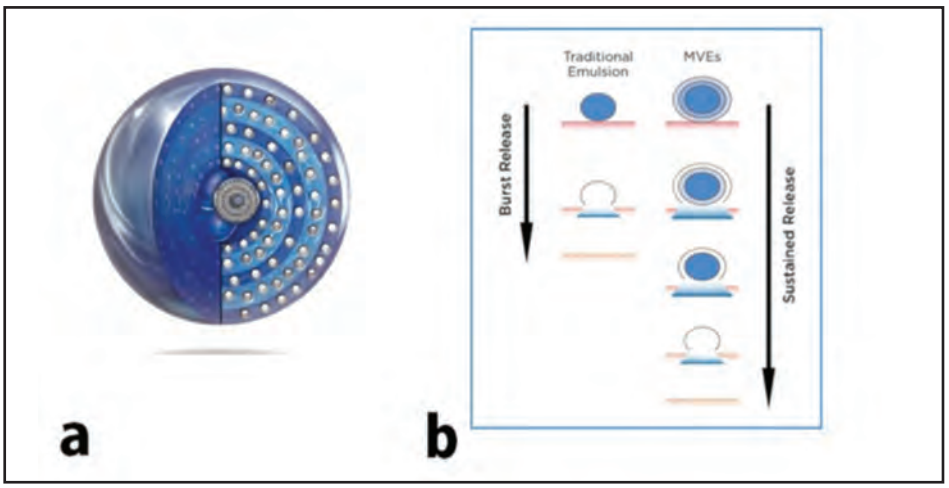

Fig. 2: Multivesicular emulsion (MVE) (a) and its sustained release mechanism of action (b).

form liquid crystalline structures, lamellar liquid crystalline, and gel structures with other chemicals formulated in the agent, strengthening the skin permeability barrier, they were incorporated into lamellar bilayer structures to enhance barrier integrity. Lastly, they penetrate nucleated layers of epidermis and the absorbed ceramides are hydrolysed to the metabolites (a sphingoid base and fatty acid), which are utilised in endogenous ceramide synthesis.[17] The metabolites amplify the production and delivery of ceramide and other lipids to the SC extracellular spaces, replenishing the lamellar bilayers essential for permeability barrier, skin hydration, antimicrobial, anti-inflammatory and cellular function.[18]

CLINICAL EVIDENCE OF CERAMIDES IN ATOPIC DERMATITIS

Based on the well-deciphered physical and biochemical roles of ceramide in AD, ceramide-dominant moisturiser seems an appealing treatment option to replenish the ceramide levels in SC of AD patients, enhancing the recovery of compromised skin permeability barrier in AD patients.[3] Numerous ceramide-dominant moisturisers with unique blends of ingredients in varying levels and ratios have been developed and introduced to the market. Although commercially available moisturisers may appear safe to be applied on the skin, animal studies have demonstrated that some products could potentially bring more harm than benefits.[19] Also, the absorption rate of ceramides often depends on the formulations and vehicle technologies.[17] Therefore, all moisturisers should be clinically proven for their safety and effectiveness before being prescribed to AD patients.

Given the heterogeneity in the study design, study population, intervention (different active ingredients and formulations), comparator used, and outcomes, this review did not pool the outcomes via meta-analysis but narratively reported individual studies. Our review shows that ceramide-dominant moisturisers are safe for children and adults with AD (Table II).

Most clinical studies have demonstrated favourable outcomes for ceramide-containing moisturisers (ceramides, pseudo-ceramides and ceramide precursors) in patients with AD, except Gupta et al.[20] and Miller et al.[39] Improved SCORAD (SCORing Atopic Dermatitis)[21,23,26,29,36,37,45], decreased TEWL[21,22,27-30,36,41,43,45], increased skin hydration[30,33-36,43-45] and reduced signs of dryness[27,28,30,31,35,43,44] were often reported after the treatment of

ceramide-dominant moisturisers. Two studies[31,40] reported a lower incidence of flare in the treatment arms while one reported a significantly shorter time to clear after the treatment of ceramide-dominant moisturisers and cleanser compared to the control arm.[25] Notably, four studies[21,24,32,33] observed inconsistent outcomes, such as positive outcomes in symptoms only but no significant difference in signs such as TEWL and skin hydration or vice versa.

This review included both cohort and randomised controlled trials. All cohort studies were limited by their non-randomisation nature and lack of control arms while most RCT studies were of small study size and short duration of follow-up. Deliberate assessments of each study's clinical effectiveness and safety are needed before prescribing ceramide-dominant moisturisers. The long-term safety and efficacy of ceramide-dominant moisturisers remained to be observed.

The findings in this review supported the guideline recommendation[2,12] for moisturisers to be incorporated as an integral part of the AD management plan, not only to improve AD signs and symptoms, but also to accelerate the skin repair process, delay incidence and time to flares and reduce the need for rescue TCS therapy.[11] Choosing the right physiological lipid moisturiser therapy with the optimal 3:1:1 molar ratio (ceramide, fatty acid, cholesterol) that suits individual AD patients is an art. Besides safety and effectiveness, moisturisers with high patient acceptability and dosing convenience could potentially improve patient compliance, providing additional value for AD patients in their roadmap to achieving long-term remission.

THE ROLE OF MULTIVESICULAR EMULSION (MVE) IN ATOPIC DERMATITIS

Over the years, several formulation technologies (Table III) were introduced to enhance the delivery of active ingredients into the skins, including moisturisers. Different formulation technologies exhibit distinct pharmacokinetic and pharmacodynamic properties which affect the therapeutic response; therefore it is of utmost importance to characterise the right formulation technologies for active ingredients intended to be delivered to the targeted sites.[46]

Multivesicular emulsion (MVE) is a unique emulsion technology that differs from the traditional water-in-oil and oil-in-water emulsion.[25] It is manufactured using behentrimonium methosulfate, a cationic quaternary amine salt emulsifier, which allows the formation of the multilamellar concentric spheres of oil and water (Fig. 2). The alternating hydrophilic and hydrophobic concentric layers encapsulate the active ingredients, such as ceramides, phytosphingosine, FA, cholesterol, dimethicone, glycerol, and hyaluronic acid, in either the lipid layers or within the aqueous compartment, depending on their compatibility.
The distinctive MVE structure allows the active ingredients to be delivered to the skin surface, rather than to be absorbed into the deeper epidermis and circulation. When used in ceramide formulations, the MVE structure allows the ceramides to be released in a controlled manner, forming a long-lasting occlusive layer. The occlusive barrier sustainably prevents TEWL, maintaining skin hydration up to 24 hours and avoiding invasion of irritants and pathogens. On top of that, MVE acts to continuously stimulate intracellular ceramide synthesis, enhancing skin permeability barrier repair.[25,28] In addition to improving the delivery of active ingredients, MVE itself displays skin barrier protective and moisturising properties[4], highlighting the potential for MVE to be used alone or as a topical vehicle to enhance the therapeutic effect of other active ingredients.

CLINICAL EVIDENCE OF MVE IN ATOPIC DERMATITIS

Given that the MVE technology is purported to provide sustainable skin hydration over an extended period, a double-blind intra-subject vehicle-controlled single open-application randomised clinical trial was conducted to compare the duration of skin hydration imparted by the MVE-based moisturisers (both cream and lotion formulations) and by three paraffin-based emollient therapies commonly prescribed in the UK among AD patients (reference). Results showed that MVE-based moisturisers provide clinically meaningful improvements in skin hydration and reduction in skin dryness that is sustained over 24 hours.[27] While patient compliance to moisturisers is prudent for changing the trajectory of AD diseases, offering sustained release once-daily application moisturisers to patients with low compliance could potentially reduce the incidence of AD flares, moving one step towards achieving long-term remission.

Besides that, several clinical studies have confirmed the clinical effectiveness and safety of MVE technology in delivering ceramides to the skin.[25-28] Compared to the areas treated with a reference cream, AD skins treated with ceramide-dominant MVE-based moisturisers were found to have greater skin permeability barrier integrity, as observed from the significant reduction in TEWL and enhanced lipid lamellar arrangement after 4 weeks of treatment. While the signs of dryness had resolved in areas treated with the MVE-based moisturisers, they persisted in areas treated with the reference cream. Signs of redness were resolved similarly in moisturiser-treated regions, suggesting that ceramide-dominant MVE-based moisturisers allow more effective and rapid skin permeability barrier repair and hydration, protecting the skin against irritation compared with the reference test cream.[28]

It is a common practice to combine the use of TCS in emollient vehicles with separate moisturisers in the treatment of AD. However, little is known about the potential interaction between moisturisers and the TCS. Upon application, the TCSs are often stored in the SC for up to 14 days depending on the vehicle formulation and the time that SC takes to regenerate. Any skin occlusion by the moisturisers may result in a second dose as the TCSs reservoir in the SC are slowly absorbed into the deeper skin layers. Besides that, moisturisers containing chemical penetration-enhancers such as propylene glycol and butylene glycol tend to increase the skin permeability and indiscriminately facilitate the permeation of TCS into the epidermis and dermis for systemic absorption. While moisturisers could potentially augment the effects of TCS, there are also concerns that moisturisers may reduce TCS responses by forming an occlusive barrier against potential irritants including TCS, or diluting the dose or

competing with the absorption of TCS. In the absence of clinical evidence, it is not possible to confirm the efficacy and safety of moisturisers and their vehicles when used in combination with TCS.

Draelos et al. conducted a randomised controlled trial on 60 subjects, aged between 5 to 80 years with mild to moderate AD, to examine the safety and efficacy of combination therapy with a high-potency TCS (i.e. fluocinonide cream 0.05%), MVE-formulated ceramide-containing moisturising cream and MVE-formulated ceramide-containing liquid cleanser. When MVE-moisturising cream and cleanser were used in combination with the highly potent TCS, the incidence of clearing at week 4 increased significantly from 15 to 76%. Greater AD signs and symptom improvement, and shorter time to clearing were also observed in the treatment group receiving combination MVE-moisturising cream and cleanser (3 weeks) compared with the treatment group receiving TCS alone (3.7 weeks). Moreover, there were no adverse events and tolerability issues reported by either the investigator or the subjects, suggesting the potential for MVE-moisturising cream and cleanser to be used concomitantly with highly potent TCS without significant interactions.[25]

Apart from effectiveness and safety, a cost-effectiveness study in the US reported that MVE-based moisturiser (CeraVe) is the most cost-effective emollient therapy, compared with other ceramide-dominant moisturisers.[53] As daily use of moisturisers is needed even after remission to achieve long-term remission, a cost-effective moisturiser could potentially improve compliance, subsequently overall patient outcomes.

Although this review may fail to capture all studies related to ceramide and MVE-formulated moisturisers due to the lack of an independent screener and publication bias, we extensively summarised the roles of ceramides and MVE technology in AD and described the most up-to-date clinical evidence of ceramide-dominant moisturisers and MVE technologies in managing AD, providing solid evidence to inform treatment decisions. Upon the availability of more clinical data, future study could meta-analyse the effect of ceramides and MVE technology in AD.

CONCLUSION

Ceramides are essential components in maintaining the skin permeability barrier and hydration, modulating skin immunity through anti-inflammatory and antimicrobial defence system, and regulating cellular functions. Most studies have shown that ceramide-dominant moisturisers are safe and effective in adults and children with AD. MVE technology offers an attractive delivery system to replenish ceramides in the SC, repairing the compromised skin permeability barrier and potentially improving patient compliance. Recommending clinically proven therapeutic moisturisers with the right ingredients (level, ratio, structure and composition), alongside an effective sustained release delivery system, to AD patients is one key strategy to successful disease control and flare prevention, potentially reducing the high disease burden to patients, families and societies.

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Serum and urine galactose deficient-IgA1 as alternative biomarkers in the management of IgA nephropathy

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ABSTRACT

Introduction: Immunoglobulin A (IgA) nephropathy (IgAN) results from abnormal accumulation of immune complexes containing galactose deficient IgA1 (Gd-IgA1) in the kidneys. About 40% of patients develop end-stage kidney disease within 20 years of renal biopsy. At present, the diagnosis and risk stratification of patients (using the international IgAN risk prediction tool) rely on renal biopsy, which is an invasive procedure. Also, treatment decisions are still dependent on proteinuria, which is not specific for IgA nephropathy. We discussed the role of serum and urine Gd-IgA1 in the diagnosis of IgAN, its association with disease progression and changes with treatment in patients with IgA nephropathy.

Materials and Methods: A systematic search of PubMed and Scopus databases was done to identify the articles that are relevant to the topic including systematic reviews and original articles.

Results: Several studies showed that both serum and urine Gd-IgA1 differentiate IgA nephropathy patients from healthy people and other glomerulonephropathies. Thus, it is useful as a less invasive diagnostic biomarker, although detection methods varied between studies with different sensitivities. There are various reports of its use as a prognostic parameter. Evidence is emerging for its use as a monitoring parameter for treatment.

Conclusion: Galactose deficient IgA1 is a promising biomarker in the management of IgA nephropathy, although a more robust and standardised means of estimation is required.

KEYWORDS:
Biomarker; galactose deficient IgA1; glomerulonephritis; IgA nephropathy; serum; urine

INTRODUCTION

Immunoglobulin A (IgA) nephropathy (IgAN) is an immune-mediated glomerular disease first described by Jean Berger in 1968.[1] IgAN in the native kidney is defined as immunofluorescence or immunoperoxidase, dominant or codominant staining for IgA in the glomeruli.[2] Characteristically, IgA exhibits dominating staining whereas IgG and/or IgM staining are less pronounced and varied.[3] The IgA deposits are primarily composed of polymeric, structurally aberrant IgA of the IgA1 subclass.[4] The global prevalence of IgAN is estimated at 2.5 per 100,000 people per year.[5] This prevalence varies widely between different regions of the world. The number is higher in Asia: Exceeding 40% of biopsy-proven primary glomerular disease in Japan and China[6,7] and least in Africa.[8]

The exact aetiology of this disease remains obscure. However, it is known to result from the accumulation of immune complexes containing abnormal IgA (galactose-deficient IgA1) in the glomeruli. Thus, its diagnosis depends on a renal biopsy and histology, which is an invasive procedure with substantial risks. The renal injury in IgAN takes different courses in different patients. While a few patients have a variable period of active disease followed by remission with complete resolution of urine abnormalities, about 40% progress slowly to end-stage kidney disease (ESKD). Others progress rapidly to ESKD.[5] Ten-year renal survival rates vary from about 85% in Caucasians and Japanese[9] to as low as 35% among Indians.[10] These variations in progression have posed a challenge to the management of patients with IgAN. It is currently difficult to prospectively distinguish progressive from non-progressive disease in the early stages. This contributes to the risk of delayed treatment for progressors and exposure to immunosuppression and its deleterious side effects for IgA patients with stable disease. Traditionally, features including hypertension, persistent proteinuria > 1 g/day, and reduced estimated glomerular filtration rate (eGFR) are used as risk factors for progression. However, these features are not specific to IgAN. The risk stratification based on the Oxford classification requires a renal biopsy, which is an invasive process with its attendant complications. Efforts to address these drawbacks have recently produced the International IgA Nephropathy Risk Prediction Tool (IIgAN-PT) by Barbour et al.[11] This tool employs clinical, laboratory and histologic data obtained at the time of the biopsy for the prediction of disease progression. It is limited by several factors. It is dependent on renal biopsy, is recommended for the prediction of a 5-year outcome, and may not be used to determine treatment.[11] To overcome these challenges, it is necessary to utilize all available techniques and search for biomarkers that can address these gaps. In this paper, we discuss the role of galactose deficient IgA1 (Gd-IgA1) as a non-invasive alternative for diagnosing and predicting

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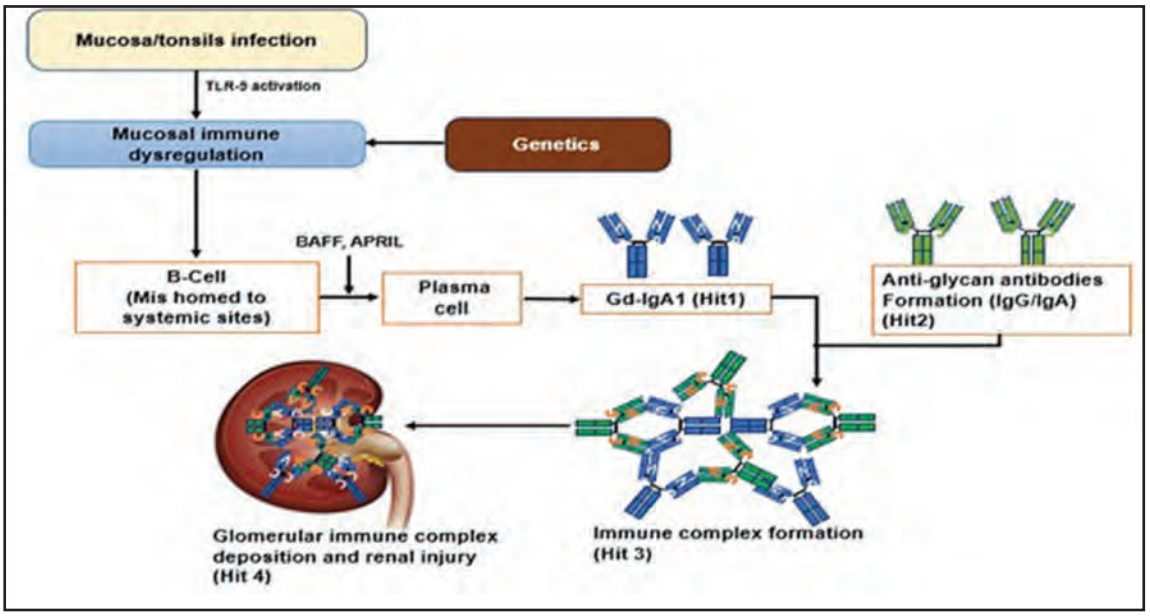

Fig. 1: Pathogenesis of IgAN. In genetically susceptible persons with mucosal immune dysregulation, repeated mucosa/tonsillar infection causes proliferation of plasma cells producing Gd-IgA1. Autoantibodies (IgG and IgA) and immune complexes are formed in response. These are subsequently deposited in the kidneys leading to renal injury.

disease progression in IgAN patients. We searched Google Scholar, PubMed and Scopus databases using several combinations of keywords. These include, 'immunoglobulin A nephropathy,' 'IgA nephropathy,' 'galactose deficient IgA1,' Gd-IgA1, glomerulonephritis, progression, biomarker, blood, urine and prognosis. The search was limited to original articles and reviews published in English. We screened and extracted those that analysed Gd-IgA1 as a diagnostic tool or its association with disease progression and treatment. The references were screened further to identify the relevant publications.

PATHOGENESIS

The exact mechanism involved in the pathogenesis of IgAN is not completely understood. Genetic predisposition,[12] environmental triggers,[13,14] and immune dysregulation[15] play different roles in IgAN (Fig 1). However, a multi-hit mechanism has been described.[16]

The Multihit Theory

Hit 1: Overproduction of galactose deficient immunoglobulin A of subclass 1 (Gd-IgA1). Normally, mucosal surface secretions contains polymeric IgA, whereas monomeric IgA is found in circulation. In genetically susceptible persons, there is an abnormal innate immunity response to mucosal infections and antigens. There is a 'mishoming' of differentiated plasma cells to the bone marrow which likely contributes to the the production of Gd-IgA1.[17] Tonsillar TLR-9 activation increases the production of interleukin-6 (IL-6) and activation proliferation-inducing ligand (APRIL), which promote production of Gd-IgA1.[18] This polymeric IgA1 lacks galactose on some O-glycans in the hinge region between the constant region domains 1 and 2 of the heavy chain. This deficiency causes the exposure of N-acetylgalactosamine (GalNac) or sialylated GalNac.[19,20] The production of aberrant IgA1 is associated with reduced activity of core1 β 1,3 galactosyltransferase (C1GalT1) and an increase in the activity of α 2,6 sialyltransferase II (ST6GalNAc-II) in IgA1 producing cells.[16]

Hit 2: The formation of glycan-specific autoantibodies against Gd-IgA1, especially IgG. The autoantibodies recognise glycan-containing epitopes on Gd-IgA1. They exhibit an A to S substitution in the complementarity-determining region 3 (CDR3) of the variable region of their heavy chains.[21]

Hit 3: Immune complex formation. The autoantibodies form immune complexes with Gd-IgA1. In IgAN patients, Gd-IgA1 exists predominantly in complexes with IgG or IgA.[22] Moldoveanu et al. provided an evidence of the role of the immune complex in IgAN pathogenesis using a mouse model. They demonstrated that the administration of Gd-IgA1 complexed with IgG from IgAN patients produced the disease. Neither uncomplexed Gd-IgA1 and its autoantibodies nor those from healthy individuals produced the disease in the models.[22]

Hit 4: Mesangial immune complex deposition. The characteristic position of the mesangial cells between the glomerular capillaries and the Bowman's capsule might explain their susceptibility to immune complex deposition. The mesangial cells in IgAN patients exhibit a mesangioproliferative phenotype and are more reactive to IgA1. These cellular inherent characteristics may be crucial for the onset of IgA nephropathy.[23]

GALACTOSE DEFICIENT IgA1 IN DIAGNOSIS OF IgAN

The gold standard for the diagnosis of IgAN is renal biopsy with immunofluorescence or immunoperoxidase showing

dominant or codominant IgA staining. Increased serum levels of IgA are known to occur in about half of the IgAN patients.[24] The serum level of Gd-IgA1 is higher in IgAN than in healthy controls, both in children and adults.[24] However, other autoimmune-mediated glomerular diseases also show increased serum levels of Gd-IgA1.[26] Gd-IgA1 is deposited in the glomerular mesangium in a manner that is not dependent on its blood concentration and is excreted in urine.[27] Urinary Gd-IgA1 levels are significantly higher in patients with IgAN compared to non-IgAN chronic kidney disease (CKD) patients.[27,28] In other studies, the urine of non-IgAN CKD showed a low level of Gd-IgA1 that was below detection on HAA-lectin Western blotting.[28,29] Although urine Gd-IgA1 is believed to be more specific for IgAN, further studies comparing blood and urine levels in the same patients are required.

IgG and IgA autoantibodies specific for Gd-IgA1 are formed in response to circulating Gd-IgA1. Serum levels of these antibodies are elevated in IgAN patients.[30,31] These antibodies are excreted in the urine in complexes with antigens, and their levels are high in the urine of IgAN patients.[29] Longitudinal studies that assess the utility of these biomarkers, especially the more specific urine components, are required.

RISK STRATIFICATION AND PROGNOSIS IN IgAN

Routine markers

Risk stratification of patients for disease progression continues to depend on renal biopsy and nonspecific measures such as blood pressure, eGFR and proteinuria. A study reported a remarkable difference in the 10-year risk of ESKD depending on the time average proteinuria (TAP). TAP of 1 g/day was associated with a 5% risk, whereas TAP > 3 g/day was associated with a 60% risk.[32] TAP appears to be the most consistent predictor, even in populations where blood pressure, eGFR and 24-hour proteinuria were reported to have no association with the renal outcome.[33] The inability to distinguish between proteinuria caused by acute inflammation around the urinary tract and chronic glomerulonephritis is still a drawback. In a study involving French patients, the incidence of dialysis or death increased with increasing blood pressure, from 5% in normotensives to 42% in uncontrolled hypertensives.[34] The 2016 updated Oxford classification of IgAN includes histopathologic lesions (mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, tubular atrophy and interstitial fibrosis, crescents [MEST-C]) which are proposed as independent risk factors for ESKD and/or a 50% decline in eGFR.[35] The S and T components have been most associated with progression, while the role of crescents in prognosis requires further clarification.[36,37] Individually, these markers are insufficient; a patient with a low risk based on proteinuria alone may have an increased risk using the MEST, and vice versa.38 This raises the need for a more specific parameter.

Galactose deficient-IgA1 and disease progression

Different studies have used various study outcomes to define disease progression in IgAN. These include a doubling of serum creatinine, a 30 to 50% decline in eGFR, ESKD, the onset of renal replacement therapy, transplantation and death. Several others use a composite of these outcomes. This is in part due to the slowly progressive nature of the disease in most patients.

Association of Gd-IgA1 and eGFR/renal failure

Elevated Gd-IgA1 levels have been associated with an increased risk of disease progression. In a study involving 91 Czechs, high levels of serum native and neuraminidase-treated Gd-IgA1 measured by lectin-dependent ELISA, predicted a faster renal function decline and poor renal survival.[30] Elevated serum Gd-IgA1 was negatively correlated with eGFR and was an independent predictor of chronic kidney disease progression in a study among 230 Korean patients.[26] Gd-IgA1 was reported to be an independent predictor of renal failure even after adjustment for eGFR and time-average proteinuria.[39] Gd-IgA1 level is also negatively correlated with eGFR.[26,40] Renal survival decreased with increasing Gd-IgA1 quartile.[26]

Association of Gd-IgA1 and proteinuria

Proteinuria is currently used as a risk factor for IgAN patients. There are conflicting reports about the association of Gd-IgA1 with proteinuria. While some studies have reported a positive correlation between Gd-IgA1 and urine protein creatinine index (UPCI),[40] others have reported no association between these parameters during diagnosis.[24]

Association of Gd-IgA1 and histology

Some studies have shown that Gd-IgA1 can be used in the risk stratification of IgAN. Higher serum and urine Gd-IgA1 levels were shown to be associated with segmental sclerosis and tubular interstitial fibrosis during diagnosis.[27,42] In a study involving 84 biopsy-proven IgAN patients, Gd-IgA1 and complement proteins were evaluated as predictors of disease progression. There were significantly elevated levels of Gd-IgA1 in patients with tubular atrophy and interstitial fibrosis. Gd-IgA1 and factor Ba independently predicted higher T scores on multivariate analysis signifying that these biomarkers were reflective of the Oxford classification of IgAN, which are reported as important predictors of ESKD.[40]

Association of Gd-IgA1 and other parameters

The human mesangial cells have a phenotype that is sensitive to stimulation with IgA1.[42] Patients with higher serum Gd-IgA1 levels may experience faster disease progression to ESKD, owing to a more pronounced mesangial cell inflammatory response and, as a result, more severe histologic changes.[27,40,42] In an *in vitro* study, primary human mesangial cells were stimulated using IgA1 derived from the serum of patients with IgAN. A higher serum Gd-IgA1 concentration was linked to a more severe mesangial cell inflammatory response, including increased MCP-1 and IL-6 production.42 Elevated Gd-IgA1 was also associated with IgAN recurrence after renal transplant.[43]

METHOD FOR DETECTING BIOMARKERS

Western Blot

Helix aspersa agglutinin (HAA) lectin western blotting after SDS-PAGE detects the presence of Gd-IgA1 in the urine samples of patients with IgAN but not in the urine samples of

Table I: Summary of laboratory findings during admission

Author	Population	Sample size	Sample	Assay method	Sensitivity	Specificity	AUC: ROC	PPV	NPV	Reference
Moldoveanu et al., 2007	Caucasian USA	153 IgAN 153 healthy controls	Serum	HAA lectin-based ELISA	76.5%	94%	0.902	88.6	78.9	24
Yanagawa et al., 2014	Japanese	135 IgAN	Serum	HAA lectin-based ELISA with neuraminidase treatment	89%	92%	0.965			30
Rahman et al., 2021	Indian	40 IgAN 38 controls	Serum	Non-lectin (KM55) ELISA	75.3%	85%	0.85	90.9	63	41
Chen et al., 2019	Chinese	1210 IgAN	Plasma	Helix pomatia-based ELISA with neuraminidase treatment	54%	90%				45
Bagchi et al., 2019	Indian	136 IgAN and 110 controls (60 non-IgA glomerular diseases, 50 healthy volunteers).	Serum	Non-lectin ELISA	74.3%	72%	0.7865	87.8	50.7	46
Jiang et al., 2015	Chinese children	72 IgAN, 30 healthy controls,	Serum	Vicia villosa lectin ELISA	87.5%	83.3%	0.976	92.6	73.5	47
Martin-penagos et al., 2021	Spanish	49 IgAN	Serum	Non-lectin (KM55) ELISA	75.5%	54.1%	0.625			48

AUC: area under the curve, ROC: receiver operating characteristics, PPV: positive predictive value, NPV: negative predictive value, HAA: helix aspersa agglutinin, ELISA: enzyme-linked immunosorbent assay

patients with other proteinuric diseases.[28] This method is, however, cumbersome and expensive.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)
The O-glycosylation patterns of IgA1 can be analysed using LC-MS/MS. IgA1 extracted from plasma using immunoaffinity beads is first de-N-glycosylated, then reduced. This is followed by trypsin digestion and O-glycopeptide enrichment through hydrophilic interaction liquid chromatography. There is a significant difference in the O-glycosylation pattern between IgAN, disease controls and healthy controls. IgAN patients had significantly lower GalNac and galactose numbers in the hinge region of IgA1. This distinguishes them from other non-IgAN CKD.[44]

Enzyme-Linked Immunosorbent Assay (ELISA)
Several lectin-based ELISA methods have been employed for the estimation of Gd-IgA1. *Helix aspersa agglutinin* (HAA) ELISA quantitation was first reported by Moldoveanu et al.[24] There are currently no standard means of estimating the Gd-IgA1 level. The different lectin-dependent ELISA methods in current use recognise galactose deficiency at different amino acid levels (serine vs. threonine). HAA-lectin-based ELISA is limited by the fact that its stability and bioactivity are dependent on the product lot. The procedure is also cumbersome. Several other lectin-based methods, such as *helix pomatia* and *Vicia villosa* lectin, have been used with different sensitivities and specificities, with the highest reported for the HAA lectin-based method (Table I).

TREATMENTS IN IgAN

There is currently no known cure for IgAN. The Kidney Disease Improving Global Outcome (KDIGO) 2021 guidelines recommended that, for all patients who do not have a variant form of IgAN, management should focus on optimising supportive care. The target systolic blood pressure is < 120 mmHg. The guideline recommends the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) as the first line for blood pressure and proteinuria control. Irrespective of hypertension status, all patients with proteinuria > 0.5 g/day should be treated with ACEI/ARB. ACEI/ARB can be titrated to the maximum tolerated dose. Other supportive therapy includes control of protein intake, avoidance of nephrotoxins, smoking cessation and control of all components of the metabolic syndrome. The addition of a 6-month course of corticosteroids is recommended in cases of persistent proteinuria (> 0.75 –1 g/day) despite 90 days of optimised supportive care and an eGFR >30 ml/min/1.73m^2. Cyclophosphamide and steroids are employed in addition to supportive therapy in cases of rapidly progressive IgAN.[49] Given that these treatment decisions are largely based on proteinuria which is nonspecific for IgAN, a more specific surrogate is required.

Galactose Deficient IgA1 in Treatment
Since Gd-IgA1 is central to the pathogenesis of IgAN, its association with therapy has been investigated in many studies. Nakata et al.[50] demonstrated a decline in serum Gd-IgA1 concentration and haematuria after tonsillectomy alone in 59% of a cohort of Japanese IgAN patients. When steroids were added to tonsillectomy, more patients improved in terms of haematuria and serum Gd-IgA1. However, the changes in proteinuria and creatinine levels were not appreciable. The study was limited by its relatively small sample size and a very short (2 to 3 weeks) study duration post-tonsillectomy. The patients who showed improvements with tonsillectomy alone were those with a higher expression of tonsillar TLR9. This indicates that the palatine tonsils are possibly a major site of cells producing Gd-IgA1. The 'mishoming' of these cells to other lymphoid organs may explain, in part, the different responses observed to tonsillectomy alone.[50] The level of Gd-IgA1 was shown to be significantly reduced after 3 to 6 months of immunosuppression (including oral and/or systemic steroid or cycloserine) in a cohort of Taiwanese IgAN patients.51 Prednisolone therapy showed a significant difference in serum levels of Gd-IgA1 from the baseline to 6 months post-transplant in a prospective study involving 36 post-transplant IgAN patients. Samples were taken before transplant, 3 months and 6 months post-transplant. Gd-IgA1 concentration was reduced with increasing doses of prednisolone. This difference was not seen with mycophenolate mofetil therapy.[52]

Another study compared the effect of standard IgAN therapy (ACEI/ARB and controlled blood pressure) and standard therapy plus rituximab on the level of serum Gd-IgA1. Neither of the patient groups had a reduction in Gd-IgA1.[53]

Novel Therapies
Gd-IgA1 is believed to be produced by B-cells derived from the mucosa-associated lymphoid tissues. These include the Peyer's patches in the ileum. A targeted release formulation of the glucocorticosteroid, budesonide (Nefecon), was formulated to be released at the distal ileum, where it may target B-cells primed to produce Gd-IgA1. NefIgArd, a phase 3 randomised, double-blind, placebo-controlled multicentre clinical trial, enrolled 199 IgAN patients who were given Nefecon or a placebo for 9 months, followed by 3 months of observation. At the end of the follow-up, there was a significant improvement in eGFR and proteinuria. There was a mean 3.87 ml/min/1.73 m^2 preservation of eGFR and 27% lower urine protein creatinine ratio levels in the Nefecon group compared to the placebo group. Although the drug was well tolerated, a major limitation of this drug is its cost.[54] The drug has been approved for IgAN treatment by the FDA.

Other B-cell targeted agents for the treatment of IgAN are under investigation. Telitacicept and atacicept are human recombinant fusion proteins that target B-cell activating factor (BAFF) and APRIL. They bind to BAFF and APRIL and cause a reduction in B-cell count. They also cause disruptions in B-cell activation, maturation and differentiation.[55] In the randomised phase II JANUS trial, Baratt et al., demonstrated that atacicept produced a significant dose-dependent reduction in serum Gd-IgA1, IgG and IgM. At 24 weeks of study, IgAN patients who received weekly 75 mg subcutaneous atacicept, had a 60% reduction in baseline Gd-IgA1. This is significant especially when compared to the 25% reduction seen in the 25 mg atacicept group and a 2% increase seen in the placebo group.[56] The patients in the atacicept groups also improved in terms of proteinuria with a relatively stable eGFR at 72 weeks.

Other drugs that inhibit the B-cell activity that have been investigated include rituximab and belimumab. Although these are capable of reducing B-cell count, they did not reduce the production of Gd-IgA1.[53]

FUTURE PERSPECTIVES

Increased serum and urine levels of galactose-deficient IgA1 are characteristic features of IgAN. More research is needed to understand the differences in levels observed across different groups, as well as their roles in prognosis and therapy. The use of Gd-IgA1 to predict the progression of the disease is currently limited by the small sample sizes in most of the studies and the difficulties in comparing the studies due to differences in the methods of assay. The reported sensitivity and specificity of the HAA-lectin-based ELISA, 76.9% and 94%,[24] 89% and 92%[29] are higher than the helix pomatia-based ELISA, at 54% and 90%[50] respectively. This makes comparison difficult and may not replace a renal biopsy yet. Thus, there is a need for a more robust and standardised method. The biomarker is yet to be studied in diverse populations to determine its utility in different populations. This is crucial considering the difference in progression among different ethnic groups. It may be possible to extend the applicability of the international IgAN prediction tool through the addition of biomarkers. In a pilot study by Pawluczyk et al, incorporating micro-RNA (miR-204) improved the predictive performance of the tool.[57] The tool may also be modified for different ethnic groups. Joo et al adjusted the race coefficient of the tool to a Korean coefficient. This improved the accuracy of the tool for that ethnic group.[58] These need to be tested in future studies.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Review of MR spectroscopy analysis and artificial intelligence applications for the detection of cerebral inflammation and neurotoxicity in Alzheimer's disease

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ABSTRACT

Introduction: Magnetic resonance spectroscopy (MRS) has an emerging role as a neuroimaging tool for the detection of biomarkers of Alzheimer's disease (AD). To date, MRS has been established as one of the diagnostic tools for various diseases such as breast cancer and fatty liver, as well as brain tumours. However, its utility in neurodegenerative diseases is still in the experimental stages. The potential role of the modality has not been fully explored, as there is diverse information regarding the aberrations in the brain metabolites caused by normal ageing versus neurodegenerative disorders.

Materials and Methods: A literature search was carried out to gather eligible studies from the following widely sourced electronic databases such as Scopus, PubMed and Google Scholar using the combination of the following keywords: AD, MRS, brain metabolites, deep learning (DL), machine learning (ML) and artificial intelligence (AI); having the aim of taking the readers through the advancements in the usage of MRS analysis and related AI applications for the detection of AD.

Results: We elaborate on the MRS data acquisition, processing, analysis, and interpretation techniques. Recommendation is made for MRS parameters that can obtain the best quality spectrum for fingerprinting the brain metabolomics composition in AD. Furthermore, we summarise ML and DL techniques that have been utilised to estimate the uncertainty in the machine-predicted metabolite content, as well as streamline the process of displaying results of metabolites derangement that occurs as part of ageing.

Conclusion: MRS has a role as a non-invasive tool for the detection of brain metabolite biomarkers that indicate brain metabolic health, which can be integral in the management of AD.

KEYWORDS:
Alzheimer's disease; magnetic resonance spectroscopy; brain metabolites; deep learning; machine learning; artificial intelligence

INTRODUCTION

Alzheimer's disease (AD) is a major neurodegenerative disorder and has been cited as the most common type of dementia in the Western population.[1] A study by Ibrahim, et al.[2] reported that vascular dementia and mixed dementia were more prevalent in Malaysia and Asian countries based on their survey at a tertiary public hospital in Kuala Lumpur, Malaysia. In view of mixed clinical findings, there is a need for advanced diagnostic imaging to provide further information to help characterise the type of dementia.

Conventionally, structural magnetic resonance imaging (MRI) is used to help diagnose AD with the support of clinical assessment and neuropsychological testing. A common finding in conventional MRI is the detection of accelerated brain atrophy in AD.[3] Furthermore, brain morphometry and seed-based analysis of resting-state fMRI (functional MRI) functional connectivity revealed that there were abnormalities in the default mode network of AD patients compared to healthy control subjects.[4]

Typical MRI findings in AD patients is a decline in both white matter (WM) volume and grey matter (GM) volume specifically beginning in the hippocampus, which becomes accelerated in this condition.[5] One of the limitations of structural MRI is that the detection of anatomical changes of neurodegeneration as evidenced by brain atrophy occurs later in the disease.[6] Thus, newer biomarkers using hybrid functional imaging such as positron emission tomography/computed tomography (PET/CT) are utilized to aid in the early detection and better characterization of AD.

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Radiopharmaceuticals utilized for PET/CT imaging in patients suspected of AD consist of two main categories, i.e., glucose-analogue tracers and amyloid protein tracers. Initially, 2-Deoxy-2-[^{18}F] fluorodeoxyglucose ([^{18}F]-FDG), a glucose analogue was utilised for PET/CT brain imaging, then followed by amyloid and tau protein PET/CT imaging, for the management of AD.[7] Although the role of [^{18}F]-FDG has been established for making the diagnosis of AD, the accuracy of the scan interpretations can decline markedly when it involves younger patients or when there are overlapping features with other types of dementia.

Consequently, this limitation was the catalyst for the development of more specific biomarkers, namely amyloid precursors. The detection of amyloid precursors is said to be able to predict the conversion of at-risk subjects to full-blown AD 10 years earlier than the onset of AD symptoms.[8] Further review of amyloid PET/CT imaging concluded that this diagnostic tool holds promise for a beneficial role in diagnosing AD in cases of inconclusive clinical findings; however, there is an inherent limitation to this modality.[8]

These limitations include its cost-effectiveness, involving ionising radiation, and practical concerns for its execution due to many variations in protocols and cut-off values for the interpretation of results.[9] Among the recent advances in MRI technology and applications, the utility of magnetic resonance spectroscopy (MRS) has been gaining momentum for improved diagnostic accuracy.

In vivo, MRS is a non-invasive tool for characterising alterations in metabolite concentration and, by extension, bioenergetic and metabolic dysfunction associated with neurodegenerative disease progression.[10] There is a need to standardise the application of MRS techniques for the diagnosis of AD to help detect the alterations in brain metabolite levels in AD patients.

Additionally, artificial intelligence (AI) has spiked in popularity in recent years including its usage in the medical imaging field. AI has led to the development of automated image classification, segmentation, super-resolution, and image reconstruction.[11] Several classes of AI have been studied extensively, including machine learning (ML) and deep learning (DL), which utilise artificial neural networks (NN) inspired by neuronal architectures.[12]

This review aims to report on the advancement in the usage of MRS analysis and MRS-related AI applications for the detection of AD. Our specific aim is to probe into the patterns of metabolite changes in the brain that represent neural inflammation and degeneration related to AD, as well as to explore the automated analysis of MRS data using AI. A literature search was carried out to gather eligible studies from the following widely sourced electronic databases such as Scopus, PubMed, and Google Scholar. The search was conducted to gather all relevant publications till August 2023.

Besides, to achieve a wider search, all relevant studies were further cross-referenced for potentially eligible studies through their bibliography. Using Boolean operators, i.e., "AND" and "OR," the following search terms were entered in the search engines of the above listed electronic databases. The keywords used were AD, MRS, brain metabolites, DL, ML, and AI.

MRS Data Acquisition

MRS utilises magnetic resonant signals obtained from a volume of interest (VOI) and performs a fast Fourier transform (FFT) to identify the types and concentrations of each metabolite within the frequency domain, i.e., the MR spectrum. Based on whether the signal is captured from a single voxel or multiple voxels, it is technically categorised as single voxel spectroscopy (SVS) or MR spectroscopic imaging (MRSI). The MR spectrum generally consists of metabolites, water, lipids, and mobile and immobile proteins within the tissue.

Each component demonstrates unique chemical shift (ppm) and J-coupling (Hz) properties based on their respective MR characteristics. This occurs via the Zeeman effect, shielding effects, and Fermi contact of the molecular structure, and can thus be distinguished within the MR spectrum.[13] In MRS, a specific VOI is selected from the anatomical image and a spectrum is collected. The spectrum has different peaks or signals from many different metabolites in brain tissue.

Each of the peaks is highly reproducible and unique. Hence, it helps to identify the specific metabolites that correspond to specific signals. The difference in frequencies occurs due to electron shielding.

There are two main sequences in MRS, namely the STEAM and PRESS sequences. In the "STEAM" sequence, three identical 90° excitation pulses are used to form a "stimulated echo" while the "PRESS" sequence uses one 90° excitation and two identical 180° refocusing pulses to create a "spin echo", which is also known as double spin echo. A comparison of these two techniques has been done, and the most obvious difference is that the spin echo-based PRESS sequence acquires double the signal-to-noise ratio (SNR) compared to STEAM, hence, it is often preferred in clinical field strength.

As the repetition time (TR) increases, the scan time required for MRS data acquisition also significantly increases, leading to unwanted additional data artefacts such as patient movement.[14] Hence, a compromise is made by performing approximately 2 – 3 pre-scans prior to the main MRS data acquisition to make the magnetisation of the metabolites to a steady state, and then data is repeatedly collected.[15] The TR commonly used at 3T is 2000 ms.

Time to echo (TE) is the duration from RF excitation for spatial localization to the resonance signal produced in the target voxel and is one of the important parameters that characterize the MRS signal. In the clinical use of MRS, the shortest TE (~30 ms at 3T, for PRESS) is commonly used.[16] This allows for the anticipation of high signal yields of all metabolites in the brain while minimising the T2-effects and J-evolution of each metabolite.

Table I: Technical features of MRS data analysis softwares

Software	Language	Fitting domain	Baseline approach	Basis set preparation
LCModel[32]	Fortran	Frequency Domain	Spline baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Tarquin[28]	C++	Time Domain	Smooth baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Osprey[29]	MATLAB	Frequency Domain	Spline baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Vespa[30]	Python	Frequency Domain	Wavelet baseline	Can be built within the program (Simulation)
INSPECTOR[31]	MATLAB	Frequency Domain	Polynomial baseline	Can be built within the program
jMRUI-QUEST[32]	Java	Time Domain	Truncated points	Can be built within the program and has user-friendly graphical interface

LCModel: Linear Combination Model, MATLAB: MATrix LABoratory by MathWorks, Inc., jMRUI-QUEST: Java-based graphical user interface magnetic resonance spectroscopy user interface quantification simultor algorithm, VESPA: Versatile Simulation Pulses Analysis

Table II: MRS-based AI classification models for Alzheimer's disease and MCI

No	Author (Year)	ML/DL	Subjects, (N)	Objective	Outcome
1	Munteanu et al., 2015[42]	ML	HC (79), AD (56)	To test and evaluate the effectiveness of machine-learning schemes for single-subject level classification of individuals affected by different stages of dementia (HC, MCI, and AD) based on ^{1}H-MRS data.	Composition of WM, GM, and CSF of the spectroscopic voxel is essential in a ^{1}H-MRS study to improve the accuracy of the quantifications and classifications, e.g., metabolite derangements were matched to regions of decreased GM in the hippocampus of AD subjects.
2	Ahmed et al., 2020[43]	DL	HC (79), AD (56)	To propose an end-to-end deep learning network for early AD and HC classification using ^{1}H-MRS raw data from the PCC area	Classification of metabolite features in PCC of patients with early AD compared to HC using Deep MRS algorithm, achieved AUC of approx. 94% for AD, with a sensitivity of 100% and a specificity of approx. 89%.
3	Kherchouche et al., 2022[44]	DL	HC (33), MCI (49), AD (29)	To propose an explainable classification framework for early AD detection using ^{1}H-MRS	Accuracy of 82% for the most challenging classification task (MCI vs. AD classification).
4	Wang, et al., 2022[45]	DL	AD (27), HC (15)	To improve the diagnosis and classification of AD using a model combining MRI and MRS metabolite levels at the frontal and parietal regions.	GABA levels in the parietal region correlated with MMSE scores of AD, and resulted in the most significant improvement in model performance, the AUC increased from 0.97 to 0.99, specificity increased from 90 to 95%.

AD: Alzheimer's disease, AUC: area under the curve, DL: deep learning, GABA: gamma-aminobutyric acid, GM: gray matter, HC: healthy control, 1H-MRS: proton magnetic resonance spectroscopy, MCI: mild cognitive impairment, ML: machine learning, MMSE: mini mental state examination

These factors work together to increase the overall SNR of the MRS signal, enabling complex metabolite profiling.[17] This is an advantage when compared to spectral-edited MRS methods using a longer TE. In AD, the commonly targeted VOI is the posterior cingulate cortex (PCC) and the precuneus because these two regions have been found to exhibit cortical thinning on structural MRI,[18] reduced glucose metabolism on PET/CT imaging and histopathological changes on brain autopsy.[19]

Even though SVS can be performed quickly and easily in most parts of the human brain, it only captures metabolite information in a specific brain region and does not provide spatial variations of metabolites in other parts of the brain. Information is generally only limited to one or two brain regions in most clinical settings. Conversely, MRSI is usually more time-consuming, but can be used to measure multiple-voxel locations simultaneously. It has a larger total coverage, hence, higher spatial information.

Advantageously, ^{1}H MRS has a high sensitivity, however, it also has the drawback of having a large water signal. This has to be suppressed to allow for the observation of tissue metabolites that are relatively smaller in representation.[20] Commonly in ^{1}H MRS, brain metabolites are observed in the millimolar concentration range, while cerebral water makes up 65-75% of the brain composition.

MRS Data Processing and Analysis

Generally, the post-acquisition workflow of SVS MRS involves a sequence of steps: 1) pre-processing for data correction, 2) performing metabolite quantification, and 3) data screening for error estimation to quantify the results. The main reason for pre-processing in MRS is due to the inevitable degradation caused by experimental imperfections such as RF slice profile imperfections, eddy currents, frequency drift, and subject motion.

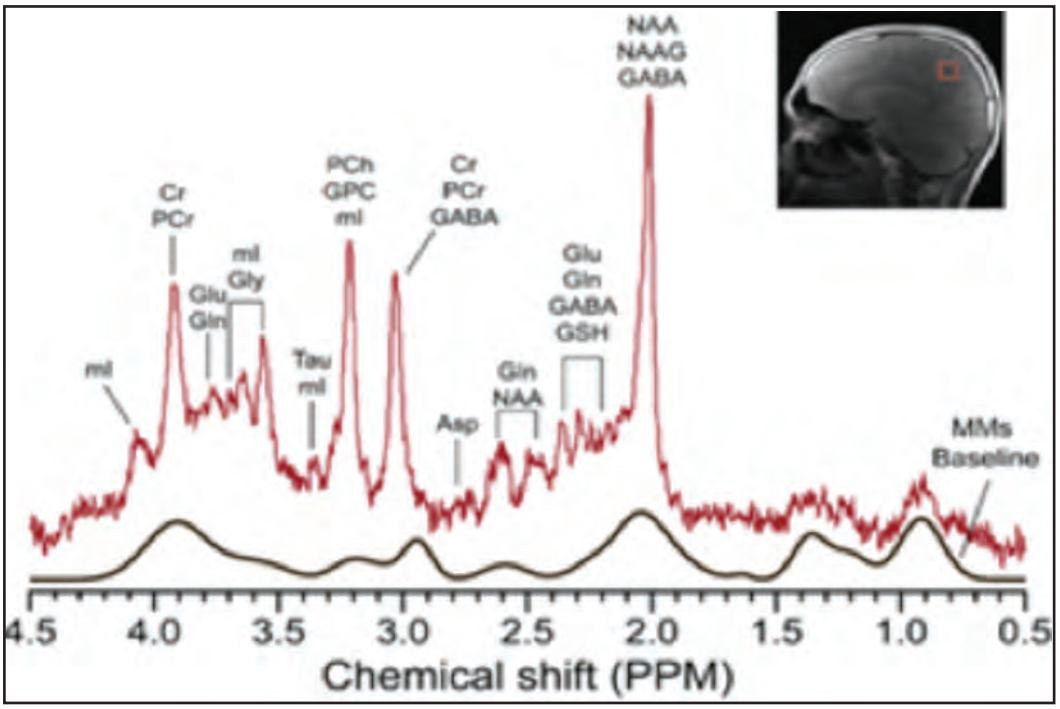

Fig. 1: Proton MR spectrum acquired at 3.0 T (TE=30 ms) of healthy older adult subject. Reproduced, with permission, from Lee.[26]

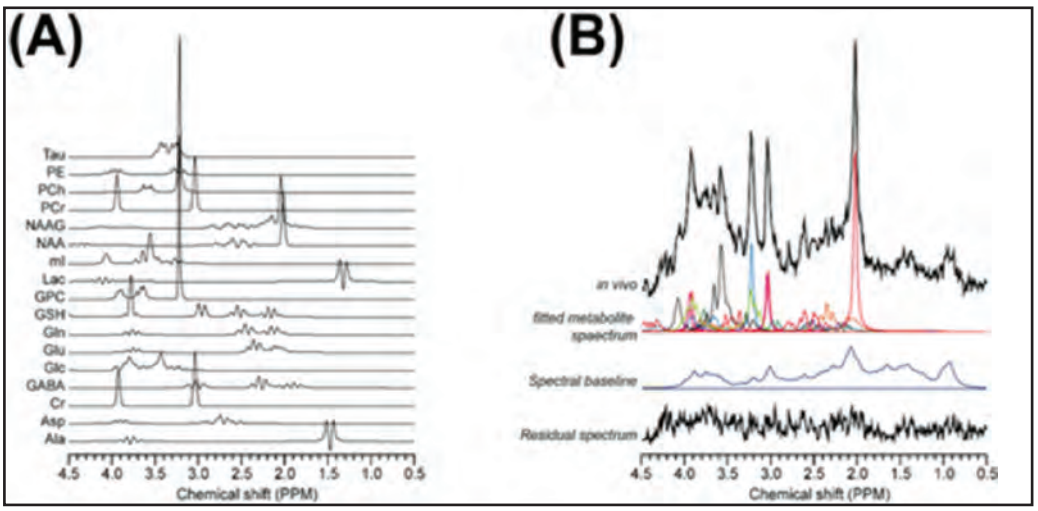

Fig. 2: Representative spectra of a metabolite basis set and quantification process. A metabolite basis set (A) incorporates chemical shifts, J-coupling, and line shapes of expected metabolites. The basis set is used for metabolite quantification from in vivo MR spectrum with spectral baseline (B). Reproduced, with permission, from Lee.[26]

Secondly, raw data are usually multi-dimensional, with multiple signal averages acquired by multiple coil channels from parallel receive array coils. Therefore, these signals must be combined to reduce the data into one dimensional single complex-valued data to be analysed. Before conducting quantitative analysis, MRS data, once merged, may undergo several pre-processing steps depending on the quality of the data.

For example, spectral distortions due to eddy currents are typically corrected using water-unsuppressed data.[21] Additional data correction may be necessary if there are severe frequency shifts or zeroth or first-order phase shifts.[22]

SNR or spectral resolution of the MR spectrum can be artificially enhanced using post-processing methods, such as apodisation and zero-filling techniques, respectively. However, the former may fail to reflect the line shape characteristics of each metabolite signal due to their respective T2 characteristics and can ultimately influence the results of metabolite quantification.[16]

The zero-filling technique remains controversial in terms of improvements in data quantification.[23] Therefore, these two functions for improving the SNR are generally used to assist in improving visual interpretation.[24] A range of software is available to perform quantitative analysis, which provides

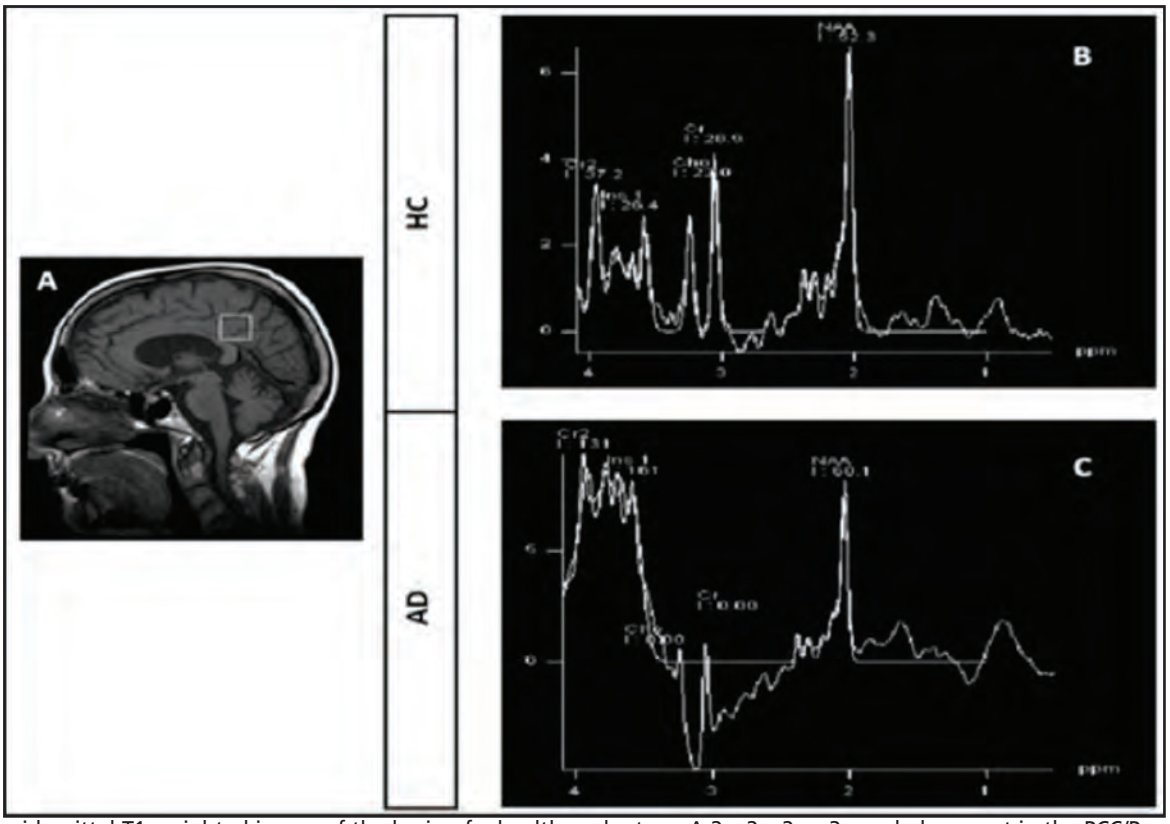

Fig. 3: A midsagittal T1-weighted image of the brain of a healthy volunteer. A 2 x 2 x 2 cm3 voxel placement in the PCC/Prec is shown in A. The difference in proton spectra and metabolites obtained from the region in healthy control and AD patients are shown in B and C. Notably, there is a significant decrease in the NAA peak in the AD subject. (This figure was reused with permission from ethical clearance received from our institutional ethical committee, reference number JKEUPM-2019-328 and Malaysian national ethical clearance number MREC (NMRR-19-2719-49105)).

high reproducibility. Nevertheless, caution needs to be exercised when comparing data from multicentre studies acquired using non-standardized protocols. Moreover, robust statistical analysis using AI could be hindered by data obtained from inferior software.

A point to consider is that the concentration of metabolites acquired using MRS is linearly proportional to the spectral peak area.[25] Under typical clinical MRS scan conditions (3T, using the shortest TE), there is bound to be overlap among metabolite spectra, including broad spectral overlap between metabolites and macromolecules in the baseline spectra. An example of a normal metabolites spectrum in healthy older adults generally has a tall N-acetyl aspartic acid (NAA) peak,[26] with some slight overlap of other metabolites that occur in lower concentrations (Figure 1).

Therefore, analysis methods based on the non-linear least squares fitting (NLSF) algorithm have been developed to address these problems, and the most common method is the Linear Combination (LC) Model proposed by Provencher et al.[27] (Figure 2). The model lays the in vivo spectrum as a fusion of pure, model spectra from each of the expected compounds in the brain.

The model also accommodates automatic phase and frequency correction and baseline correction. With the proper adjustment of each scanner and by using correct model solutions, the program returns metabolite concentrations (relative to an unsuppressed water signal or other internal metabolite references such as total creatine (tCr = creatine (Cr) + phosphocreatine (PCr)) or total choline (tCho = glycerophosphocholine (GPC) + phosphocholine (PCh)) as well as estimates of ambiguity.[27]

In NLSF, each metabolite's input to the overall spectrum is modelled as a single response function called the "basis set". Along with the LC Model, the development of software based on the NLSF algorithm has been steadily ongoing, and the following are representative examples: Tarquin,[28] Osprey,[29] Vespa,[30] INSPECTOR,[31] and jMRUI-QUEST among others have been designed by Graveron-Demilly,[32] Oeltzschner et al.,[33] Soher et al.,[30] Gajdošík et al.,[34] and Jabłoński et al.[35] as shown in Table I.

While attempts have been made to develop techniques for metabolite quantification and to apply MRS clinically, there are several limitations that make it difficult to use as a clinical tool. Specifically, the standard deviation of quantification results based on Cramér–Rao Lower Bound (CRLB) is commonly used as an error estimation indicator for quality control (QC) of results obtained using the NLSF method.

For example, according to the LCModel, it is not recommended to use results with a CRLB of 20% or more for statistics.[36] However, such CRLB-based QC can unintentionally lead to statistical bias, and furthermore, the

CRLB itself does not directly reflect the absolute error of quantification.[37] Additionally, there are large discrepancies in the analysis results between different software using various NLSF algorithm methods.

AI in Quantitative MRS Analysis.

The benefits of using AI have been widely discussed in the medical literature.[38] By using AI algorithms that resemble the network of neurons of the human brain, DL has been able to demonstrate excellent capability in pattern identification and denoising, thus providing a good-quality image for disease diagnosis, especially in AD. To address the technical issues in MRS analysis along with advances in AI, recent efforts in the MRS field have attempted to develop metabolite quantification techniques based on DL and ML.

Technically, various algorithms based on random forest,[39] autoencoder-based,[40] conventional convolutional neural network (CNN),[41] and Bayesian (BNN) have been developed, suggesting the feasibility of MRS analysis in clinical settings through these technical developments. On the other hand, one of the most significant technical challenges in applying ML/DL is to provide "uncertainty information" about the real-world data targeted inferences of the pre-trained model, allowing users to perform QC on the actual predicted quantification results.

Nevertheless, quantitative research achievements still lack empirical data on various diseases. Hence, further research is required to make MRS-based metabolite quantification potentially useful in a wide range of diverse clinical applications with the aid of ML/DL in the future.

AI in MRS for the Classification of Alzheimer's Disease Patients.

The use of AI techniques to improve MRS quantification has been increasingly adopted, along with the application of ML/DL for the classification of patients with cognitive impairment using MRS data by Munteanu et al.,[42] Ahmed et al.,[43] Kherchouche et al.,[44] and Wang et al.[45] as shown in Table II. The application of ML/DL in MRS can provide a potential avenue for early detection and treatment of dementia. For example, in the pioneering study by Munteanu et al., which was an MRS-AI-based classification of AD, multilayer perceptron was used on MRS data of 260 older adults, and the results extracted features such as metabolite derangements in the hippocampus that were similar to those of previous studies using structural MRI data.[42]

Recently, the development of end-to-end deep CNNs by Ahmed et al. and Kherchouche et al. have further advanced the field of dementia disease detection.[43,44] These types of CNN models have been able to accurately detect the presence of dementias using MRS data, suggesting that DL can be a powerful diagnostic tool by achieving 93.3% accuracy in 135 subjects (AD: 56, healthy control (HC): 79)[43] and 94% accuracy in normal and mild AD group and even 90% accuracy in normal and mild cognitive impairment (MCI) group in the diagnosis of these conditions.[44]

Furthermore, a study conducted by Wang et al.[45] demonstrated the effectiveness of classifying dementia patients by using both MRS and structural MRI data, achieving an accuracy rate of 96% to 98%, depending on the feature domain characteristics used in the classification. Hence, a noticeable focus lies in enhancing the accuracy of classifiers, limited by little to no discussion on generalisability, MRS data quality control, or broad applicability. Unfortunately, many studies employ analogous model architectures with scant comparisons between model structures.

Consequently, there is a need for multidisciplinary integrated research using ML/DL that not only improves the accuracy of metabolite quantification results inherent in MRS data but can also distinguish and link the severity of cognitive impairment with the pattern of the spectral data.

MRS Data Interpretation

Multiple metabolites are detectable at 1.5 or 3T with ^{1}H MRS in a normal human brain, including the prominent resonances of total NAA (tNAA), total creatine (tCr), total choline (tCho), and signals from myo-inositol (mI), glutamate and glutamine (Glx). Lactate is not usually seen in normal brains but is detectable in pathologies that cause its concentration to increase such as in brain abscesses and necrotic tissue.[17,46] Moreover, using MRS, one can detect characteristic patterns for AD because it has a unique metabolite pattern compared to other dementias when regional differences are taken into consideration.[47]

Total N-Acetyl-Aspartate

Total N-acetyl-aspartate (tNAA) is the largest metabolite signal in the spectrum[26] and is made up of the sum of N-acetyl-aspartate (NAA) and N-acetyl-aspartatyl-glutamate (NAAG). A very prominent signal at 2.01 ppm is usually shown by NAA corresponding to its methyl group.[20] "Neuronal marker," is another name given for NAA. This is because immunocytochemical studies have suggested that NAA is mostly tethered to the neurons, axons, and dendrites within the central nervous system. The decrease in NAA is one of the main findings in AD,[48] which is attributed to the loss of neuronal integrity that occurs in cells that undergo neuroinflammation and degeneration, as can be seen in Figure 3.

The most common VOI detected for the reduction of NAA has been reported in the medial temporal lobe, hippocampi, and PCC.[48] Even though NAA reduction is a well-known observation in AD, the outcome or findings are not consistent with those subjects having MCI, which is the prodromal stage of AD. Several studies claimed significant similarities between MCI cases and AD, whereas other studies found a significant difference between MCI and AD but not between MCI and HC.[49]

Total Creatine

Other than that, total Creatine (tCr) (3.01-ppm singlet and ~3.9-ppm singlet) arise from methyl and methylene group, respectively and is made up of the sum of creatine (Cr) and phosphocreatine (PCr), also known as energy metabolites. tCr is commonly used as an "internal reference" to quantify

other neurochemicals.[26] In a normal healthy brain, the level of tCr is found lower in WM compared to GM. Moreover, a greater level of tCr is found in the cerebellum in comparison with the supratentorial regions.

Total Choline

Referred to as choline-containing compounds (tCho) (3.21 ppm singlet arise from three identical methyl groups) in the human brain, it is involved in phospholipid synthesis and degradation, reflecting cell membrane turnover. tCho is mainly composed of Glycerophosphocholine (GPC) and Phosphocholine (PCh) and plays different functional roles in cell membrane formation and degradation. However, so far, there have been no consistent reports on the changes in Cho in either AD or MCI.

Myo-Inositol

Another commonly detected metabolite is myo-Inositol (mI). This metabolite produces one of the larger and strong coupled signals in short echo time spectra, which produces a signal at 3.5–3.6ppm. mI is much more abundant in glial cells as compared to neurons, and therefore it is increased in association with an increase in the glial component. Several recent studies related to MRS focused on MCI and AD have shown abnormal mI metabolite profiles. For example, a meta-analysis of MC and AD indicated decreased NAA and increased mI levels associated with MCI and AD, respectively.[49] Besides, NAA reduction and mI increase in AD compared to MCI and HC have also been detected, and this contributes to an increase in specificity and accuracy of the clinical diagnosis (100% for distinguishing AD from HC).[50]

Glutamate and Glutamine

Glutamate (Glu) and glutamine (Gln) (2.1–2.4- and 3.7-ppm multiplets) metabolites are complex (Glx = Glu + Gln); hence, their peaks are difficult to be distinguished, both from each other and from other compounds. At higher magnetic fields, like those used in preclinical studies, they can sometimes be resolved, depending on the spectral quality, but in general, it is difficult to obtain reliable measurements of these metabolites separately.[20] The most common brain region that shows a reduction in the level of Glx in AD is the anterior cingulate cortex, hippocampi, medial temporal lobe, and PCC.[49]

γ-Aminobutyric Acid and Glutathione

The primary inhibitory neurotransmitter in the brain is known as γ-aminobutyric acid (GABA) (1.9-, 2.3-, and 3.0-ppm multiplets). Due to the nature of the metabolites such as being very small and/or having overlapping peaks they are very hard to be detected routinely.[26] The concentration of GABA and glutathione in a normal brain are at relatively low levels (1.3–1.9 mmol/ kg weight),[13] which could also be a contributing factor to the difficulty of peak detection. Both GABA and Glutathione (GSH) have been reported to be observed at lower concentrations in AD compared to cognitively normal controls.

Metabolite Ratio (Semi-Quantitative Method)

Metabolite ratios have some instinctive benefits, such as accounting for partial volume effects or enhancing spectroscopic "contrast" in conditions where metabolites may change in opposite directions (e.g., tCho increases, tNAA decreases), however, the ratios may become inaccurate if all the metabolites are changing simultaneously.[26] The metabolite ratios that we commonly refer to are tNAA/tCr, tCho/tCr, mI/tCr, mI/tNAA, tNAA/mI, and Glx/tCr. AD patients exhibited a regional decrease in tNAA/tCr in the PCC and superior temporal lobe, and this reduction in demented patients compared with controls is due to the accelerated axonal damage.[50] Most of the previous research on AD and MCI have reported tNAA/tCr ratios to be consistently decreased.[50]

The reduction is caused by neuronal loss in addition to non-structural and physiological changes associated with impaired mitochondrial activity. Common findings in metabolite ratio for AD diagnosis are an increase in mI/tCr in AD followed by a decrease in tNAA/tCr and an increase in the ratio in tCho/tCr.[50] In addition, a systematic review done by Piersson et al.[50] had concluded that alterations in tNAA/tCr, tNAA/ml, and ml/tCr ratio may be potentially useful biomarkers that may highlight functional changes in the clinical stages of AD.

Automated Analysis of MRS Spectra

ML and DL have the potential to control spectral quality management and metabolite quantification, providing an automated analysis of MRS data. A study by Lee et al.[41] which was designed to develop a method for metabolite quantification with simultaneous measurement uncertainty estimation in DL-based 1H-MRS of rat's brains concluded that this method can be used for non-invasive metabolomics without additional data post-processing such as spectral fitting. They further stated that DL has great potential for the quantification of brain metabolites using 1H MRS data.

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A new enigma: doping in E-sports

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ABSTRACT

Electronic sports (e-sports) is a growing entity that is estimated to be valued at USD $200 billion by the end of 2023. With the rapid rate of growth, it will come to a point that e-sports will need to be regulated including regulatory mechanisms of fair play, which includes sports doping. With the emergence of substances that provides unfair advantages in terms of concentration, staying awake and preventing anxiety including tremors, there is a need to regulate doping in e-sports. However, due to the nature of the sport, it might not be as straightforward to regulate as other sports.

Doping has always been a heated debate within the field of sports.[1-3] From the famous admission of Lance Armstrong, to the time of Olympic medals being stripped-off athletes like Rick DeMont for being tested positive for banned substances, the list goes on. Doping in sports is defined as consuming a substance that is either illegal for particular sports for offering the athlete an unfair advantage over their opponents or the substance might just be illegal by law altogether.[1] Though there might be an avenue for Therapeutic Use Exemptions (TUE) for certain medications that are classified as banned substances, there is a need to regulate it so that these strict regulations do not affect an athlete's health nor should it be an avenue for an athlete to consume substances and obtain an unfair advantage over their opponents.[3]

Electronic sports (e-sports) is a growing entity that is estimated to be valued at USD $200 billion in 2023.[4] Unlike conventional sports that have a time and place, e-sports are readily accessible to a person intending to engage in it, making it appealing to the larger masses of people especially the youths of today. With the rapid rate of growth in e-sports, e-sports will evolve with an official need to be regulated just as regular sports.[5,6] One of the regulatory mechanisms which every sport has undergone is fair play, which will include sports doping—sampling for substances and consequences for breaching the law.[3,5,7] Though it might be non-sensical to think that doping might have any effects on the outcome of e-sports—it is far from the truth.[3,6] With the emergence of substances that provides an unfair advantage for e-sports athletes in terms of concentration, staying awake and preventing anxiety including tremors—a regulatory need has become more apparent.[2,3,6,7]

The World Anti-Doping Association (WADA) have divided the classified substances that are banned by two categories: in-competition and out-of-competition detected substances.[6] This list is compiled and readily available for reference at: https://www.wada-ama.org/sites/default/files/2022-09/2023list_en_final_9_september_2022.pdf. However, certain banned substances are more relevant to certain sports than others. For example, beta-blockers, a drug that is used to reduce heart rates and tremors in cases of anxiety, are abused in sports that require the athlete to have a steady hand (i.e. archery).[8] Though the substance might not be life-threatening when consumed or against the law of the land, it might provide an unfair advantage to the athlete when it comes to competition thus causing it to be a banned substance.[5]

In terms of e-sports, it is known that players tend to need to have long hours of concentration, need to have proper eye and hand co-ordination, stable hand control and a state of calmness in order to perform better in an e-sports event.[2,3] That became another controversy in 2015 when an e-sport professional athlete openly admitted to his team utilising substances such as amphetamines (and/or their byproducts) for the purpose of improving their focus during events whilst other athletes have admitted in abusing marijuana for the purpose of staying awake with temporary paranoia to perform better.[2,3,9] There have also been reports of athletes consuming beta blockers to calm themselves before intense matches and to also mask the tremors from anxiety so that they perform better in e-sports.

Though this is currently under the prerogative of the e-sports organisers to screen athletes for doping, there is a strong need for international standardised regulations to govern all forms of doping for e-sport competitions.[5] In Malaysia, the popularity of e-sports has surged notably, bolstered by the country's enhanced performance at both regional and international gaming competitions. This was evidenced by the recent silver medal won by the national team in the Asian games. However, very little has been published or spoken about doping in e-sports here in Malaysia. It was comforting to know that in Malaysia, since 2005, there have been no e-sport athletes who were involved in substance abuse (https://www.adamas.gov.my/ms/2005). However, the National E-Sports Development Guidelines (NESDEG) vaguely referred to the Anti-Doping Association of Malaysia (ADAMAS) and WADA guidelines that still had a large grey area as far as e-sports doping is concerned. We would like to believe that screening for substances was conducted (though it was strongly encouraged by NESDEG) and no substance abuse was detected. However, with the growing stature of the game, especially with the money involved in sponsorships and game prizes, it might be a good time to start regulating

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the e-sport scene—led by the Ministry of Youth and Sports here in Malaysia.[5] The authors are also concerned that areas that are commonly used for e-sport training like cybercafés (those with good equipment and fast internet access) are common areas where substance abuse occurs.[9] Thus, the need for a swift control and regulation doping amongst e-sport athletes is now even more important than before.

However, due to the nature of e-sports, it might not be as straightforward to regulate it as other sports. As some of these tournaments are competed online, it might be difficult to detect substance abuse, especially after the gaming competition.[3,5] To overcome this at an international stage, e-sporting events are being moved to fixed on-site venues. This was said to prevent unfair external advantages like online internet connectivity stability and speed. However, it also served as an opportunity for organisers to ensure competitions were played fairly by screening athletes for substance abuse—before, during and after events.5 We must also be wary that e-sports athletes are at higher risk of addiction, Attention Deficit Hyperactivity Disorders, visual impairment, neurological impairment and ergonomic disorders like carpal tunnel.[2,9] This might cause athletes to suffer from in-competition injuries requiring medications that may or may not be part of the banned substances. This might also be viewed as a window of opportunity for some athletes to consume banned substances as an excuse for a medical condition.[2,6] Will this also be the first sport to consider caffeine consumption as a potential substance abuse as athletes can be perceived to obtain an unfair advantage to stay alert for longer hours? [7,10] It is said that consumption of caffeine at 3 mg/kg of body weight might benefit sports performance.[10] Will that make it a substance providing an unfair advantage to e-sports athletes? E-sports may also heavily involve musculoskeletal, mental health disorders (i.e. "Gaming Disorders", behavioural disorders, attention deficit hyperactive disorders, gaming addiction, etc) and substance abuse that might be classified under the circumstances of general occupational health-related injuries/diseases.[2,3,5-7]

E-sports and doping are areas that sports and addiction medicine should focus on. Due to the grey areas and the complexity of the gaming mechanism, the regulatory bodies must engage with experts and stakeholders to ensure e-sports are free of potential doping.

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CONFLICT OF INTEREST

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Sleep quality in diabetic patients depends on numerous influencing factors

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Dear Editor,

We read with interest the article by Saparwan et al. on a cross-sectional study of sleep quality in 319 patients with type 2 diabetes using the Malaysian version of the Pittsburgh Sleep Quality Index (PSQI-M) with a cut-off of >5 for poor sleep quality and Depression Anxiety Stress Scale-21 (DASS-21).[1] The mean PSQI-M was 4.04, and 23% had poor sleep quality.[1] Poor sleep quality has been associated with Indian ethnicity, separation or widow status, nocturia and depression.[1] It was concluded that the prevalence of poor sleep quality was lower compared to other studies and could be improved with improved treatment of all etiological factors.[1] The study is impressive, but some points should be discussed.

Although the exclusion criteria included shift work, travelling across time zones within a month, pregnant women, breastfeeding mothers, type-1 diabetes, mental illness or taking psychotropic medication of any kind, a sleep disorder diagnosed before diabetes and patients with endocrine disorders (e.g. thyroid disease), chronic glucocorticoid use and heart failure, several other factors that influence sleep quality were not taken into account, and corresponding patients were obviously not excluded.

Poor sleep quality is multi-causal and can also be due to neurological disease such as seizures from diabetic encephalopathy,[2] ischemic stroke due to diabetic macro-angiopathy,[3] Parkinson disease,[4] restless legs, neuropathic pain in patients with diabetic polyneuropathy, cardiac arrhythmias, peripheral artery disease due to diabetic microangiopathy, lung disease such as chronic obstructive pulmonary disease (COPD),[8] sleep apnea syndrome, urological diseases such as pollakisuria or nocturia, orthopedic disease (e.g. musculoskeletal pain), gastroenterological disease (e.g. nausea, gastritis, reflux), immunological disease such as arthritis, colitis, Crohn's disease, or due to other concomitant diseases.

Sleep quality also depends heavily on lifestyle and exogenic factors, such as eating habits, timing of water and food intake, taking illegal drugs and the use of adrenergic stimulants, such as nicotine, caffeine, cola, Red Bull or abuse of alcohol. The noisy sleeping place, humidity, the noisy workplace, the personality structure and the pattern of social interactions were also not taken into account. These potentially influencing cofactors must be included in the analysis and require detailed discussion.

Another strong factor influencing sleep quality that is not considered is current medication. Although those taking psychotropic drugs such as hypnotics, sedatives, antidepressants, neuroleptics or steroids were excluded from the study, there are several other drugs that can affect sleep quality, such as adrenergic drugs, antiepileptics, anti-Parkinson drugs, beta-blockers, choline-esterase inhibitors (e.g. donepezil, rivastigmin, galantamine), decongestants and medicines containing caffeine. In order to assess whether other co-medications affected sleep quality or not, it is important to know how many of the included patients were taking one of these medications.

A limitation of the study is that the test–retest variability of the PSQI-M and DASS-21 was not assessed. In particular, depression scores can vary significantly between different tests at different times.

In summary, the excellent study has limitations that should be addressed before drawing final conclusions. Clarifying the weaknesses would strengthen the conclusions and could improve the study. Poor sleep quality in diabetics may be due not only to hormonal imbalances that increase appetite, blood sugar and insulin resistance and can lead to obesity and poor blood sugar control but also to several other complications of diabetes or co-morbidities. Neurological co-morbidities in particular can have a strong influence on sleep hygiene. Therefore, it is recommended that diabetics with poor sleep quality undergo neurological evaluation, including cerebral imaging, electroencephalography and nerve conduction studies, and screen their current medication for side effects such as sleep disturbance.

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